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INFANTILE MORTALITY AND BACTERIOLOGIC INVESTIGATIONS OF THE EFFECT OF PROLONGED LABOR ON THE BABY

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THE past decade has witnessed a definite reduction in the maternal mortality rate of the United States and, it may be said, that this decrease has been recorded in almost all areas of the country. An analysis of the factors responsible for this noteworthy improvement in American obstetrics, as applying to the maternal end results, reveals, we believe, that more adequate teaching of medical students, better hospital training of graduates, and concerted efforts by federal, state, county, and city organizations, both lay and professional, are among the major causes. Unfortunately, however, no comparable reduction in fetal or neonatal mortality has been accomplished; perhaps because attention often has been focused upon the maternal results, almost to the exclusion of consideration for the offspring. We are of the opinion that the next decade should witness equally concerted efforts, on the part of all concerned, to reduce fetal mortality.

In this paper we shall employ the term "infantile mortality" to include all full-term and premature (1,500 to 2,500 Gm.) infants, stillborn, or dying within fourteen days following birth. During the past ten years we have made determined efforts to reduce infantile

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mortality, and we have investigated the cause of infant deaths that have not been explained by trauma, congenital abnormality, asphyxia, maternal disease or some other known cause. Most of the clinical reports that appear in the literature on this subject include a relatively large number of infantile deaths that are not adequately explained. In 1934 we started taking blood cultures from the heart of stillborn infants immediately following delivery. As time progressed it became evident that the great majority of positive blood cultures were in infants born following prolonged labor where there was definite clinical evidence of intra-partum infection. In the first section of this paper we shall present a brief summary of our infantile mortality and various associated factors. In the second section we shall review a group of babies who had positive blood cultures at the time of delivery.

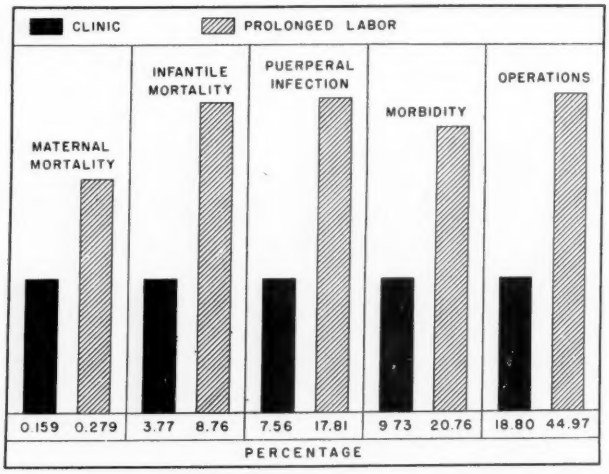

Fig. 1.

Material

In the period Sept. 1, 1932, to Aug. 1, 1942, there occurred 25,574 term and premature deliveries in the service of the Lying-in Hospital. There were 73 maternal deaths, or a rate of 2.64 per thousand deliveries. If maternal deaths of patients admitted post partum and deaths occurring in the home are omitted, the total number of maternal deaths is reduced to 67 and the rate to 2.42 per thousand deliveries. If patients dying before delivery, abortions, home delivery, and patients admitted post partum are excluded, there remain 44 deaths, or an incidence of 1.59 per thousand deliveries. There were a total of 1,041 (3.77 per cent) infantile deaths. The morbidity was 9.73 per cent and the incidence of puerperal infection 7.57 per cent.

For reasons previously stated, our attention has been primarily directed to the study of prolonged labor, which we arbitrarily have defined as labor lasting more than 30 hours. Consequently, we analyzed the percentage incidence of puerperal infection, maternal morbidity, maternal mortality and infantile mortality for labors of 30 to 36 hours,

37 to 48 hours, 49 to 60 hours, and for labors longer than 60 hours where delivery terminated spontaneously as well as by operative means. It at once became apparent that there is an increase in all of these factors as the duration of labor is increased, but even more marked is the difference between the incidence of these various factors between the spontaneous and operative groups. The latter group has an incidence of puerperal infection and morbidity of two to nearly four times that of the former, while the number of maternal and infantile deaths is greatly increased in the operative group.

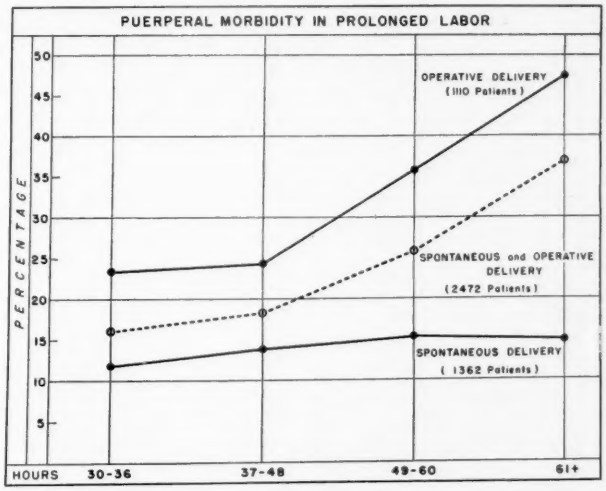

Fig. 2.

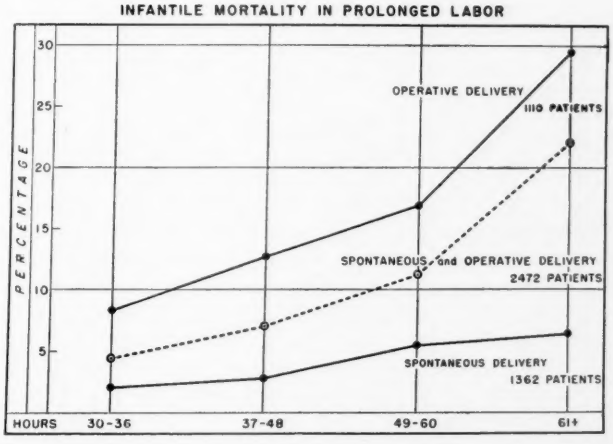

Fig. 3.

Fig. 1 illustrates graphically the great increase in maternal mortality, infantile mortality, puerperal infection, morbidity and the operative incidence in prolonged labor as compared to the incidence of these factors in the Clinic as a whole. The complications referred to are, in gen-

eral, more than twice as frequent in the prolonged labors as compared to the incidence in the Clinic as a whole. Fig. 2 shows that the great increase in puerperal morbidity is due chiefly to a very large increase of morbidity in the operative deliveries, while the increase in the spontaneous deliveries is relatively small. From a numerical point of view these curves are constructed from data that are quite comparable. The dotted line on this chart illustrates the combined rate for both the spontaneous and operative deliveries and demonstrates that the increase is caused primarily by the high rate in the operative group. It will be noted in general that the increase is not very marked prior to the elapse of 48 hours after the onset of labor. A very sudden increase occurred in the labors lasting 49 to 60 hours and a still further increase in those labors lasting longer than 60 hours. Fig. 3 illustrates the infantile mortality in labors lasting longer than 30 hours and the curves are quite comparable to those shown in the previous chart; namely, the number of infantile deaths in prolonged labors terminated by spontaneous delivery is relatively small in labors lasting up to 48 hours, and this number is only slightly increased where the labors extended up to 60 hours or even beyond that period of time. On the other hand, the upper curve in this graph shows a marked increase in infantile mortality where labor was terminated by operative means in the 30 to 60 hour group, and a steady increase in this rate until in the labors extending beyond 60 hours the mortality rate approaches 30 per cent. Again, the dotted line in the middle, which illustrates the infantile mortality in both spontaneous and operative deliveries, shows a definite increase which is caused largely by the deaths following operative deliveries. It is only fair to state at this point that the unfavorable results following the termination of prolonged labor by operative means may have been, in very many instances, absolutely necessary and unavoidable. Also, quite frequently, the baby was dead at the time the operative procedure was undertaken. On the other hand, the data illustrates graphically that the results are very much better if labor terminates spontaneously. This applies equally to mother and child. Accordingly, it would appear that prolonged labor per se should not be an indication for the operative termination of any labor.

A breakdown of the operative deliveries into three groups, namely, cesarean section, forceps, and breech, shows that in prolonged labor the incidence of cesarean section is approximately one-half that of the Clinic incidence as a whole. The frequency of forceps operations is approximately two and one-half times greater following prolonged labor as compared to that in the entire clinic, while the incidence of breech extraction is significantly increased. The infantile mortality following these three operative procedures in prolonged labor reveals a substantial increase following all three procedures, most marked in the forceps and breech extraction groups. It is significant to note at this time the relatively high infantile mortality following cesarean section in prolonged labors. Such indications for this operative procedure as premature separation of the placenta and placenta previa are very infrequently encountered in this group and, accordingly, are not the factors that would tend to increase the infantile mortality. It is also important to note that the mortality following forceps operations is more than four times as great where the labor is 60 hours or longer as compared to labors of 30 to 36 hours. The mortality following breech extraction amounts to one-third of all babies delivered by this means where the

labor lasts 60 hours or longer. This information is illustrated graphically in Fig. 4. The curve for cesarean section is omitted because of statistical unreliability owing to the small number of cases as compared to the relatively large number terminated by forceps and breech extraction.

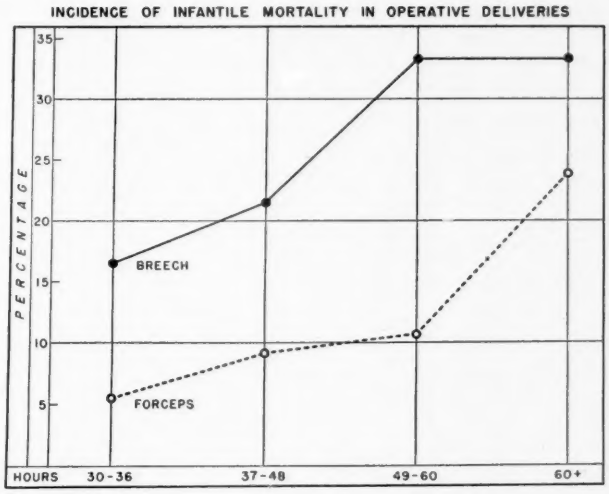

Fig. 4.

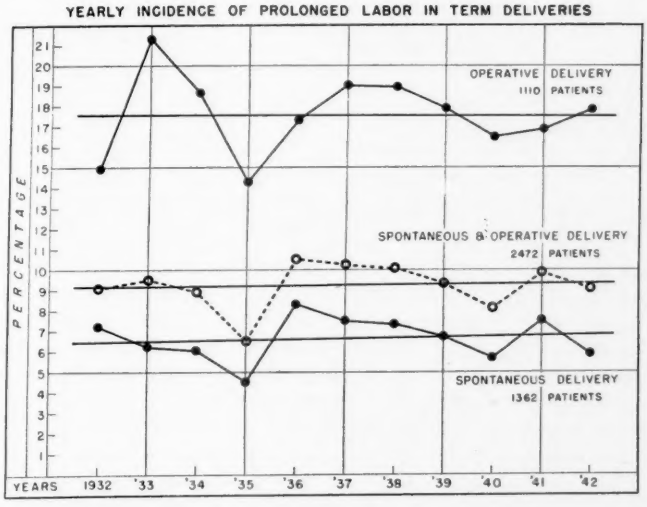

Fig. 5.

With this information at hand, which is quite disturbing, it becomes apparent at this point that we are not reviewing our good results but rather our experiences with some of our most trying obstetric problems. We will now proceed in an attempt to discover whether the incidence of prolonged labor is decreasing or increasing and whether the results are improving or not. Fig. 5 illustrates the yearly incidence of prolonged labor in term deliveries during the years from 1932 to 1942, re-

spectively. Observations for 1932 and 1942 do not cover the entire year, but they are calculated on a percentage basis and so are quite comparable. It may be seen, then, in Fig. 5 that the number of spontaneous and operative deliveries remains essentially the same throughout this ten-year period of time. The upper and the lower line illustrate the incidence in the operative and the spontaneous groups individually, and the middle curve represents the sum of both. The mean of each of these graphs is approximately a horizontal straight line. In other words, there has been no change during this period of time in the incidence of spontaneous or operative deliveries following prolonged labor.

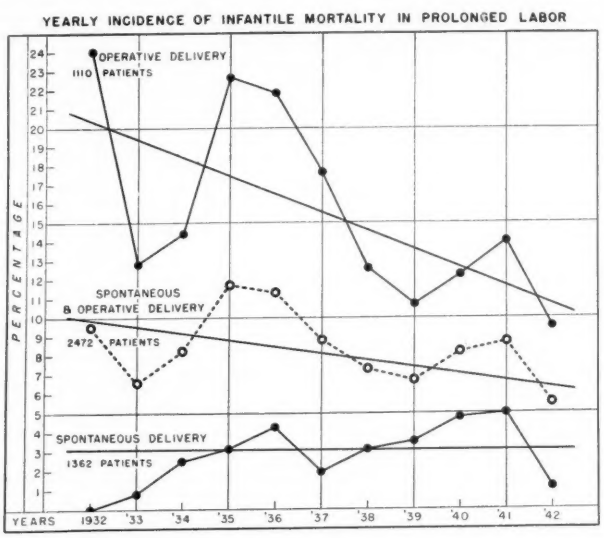

Fig. 6.

We then investigated the yearly incidence of infantile deaths in term deliveries following prolonged labor during the same period of time. This information is graphically illustrated in Fig. 6. It becomes apparent that the infantile mortality in spontaneous delivery following prolonged labor has remained relatively constant or increased slightly during this entire period of time and, in fact, this data may be expressed as a horizontal straight line. This is in marked contrast to the upper curve on this chart which illustrates the infantile mortality following operative delivery. A mean line which represents the approximate trend of this curve shows a very definite and progressive decrease from 1932 to 1942. This decrease is, accordingly, reflected in the combined curve represented by the middle dotted line and the decrease here is accounted for entirely by the decreased incidence of infantile mortality in the operative group. It then becomes evident that while the incidence of spontaneous and operative deliveries in prolonged labor remained constant, yet the incidence of infantile mortality in operative deliveries decreased significantly during the same time period.

In order to find a solution to this problem, we investigated the incidence of prolonged labor by years according to the duration of labor. Interestingly enough, the results of this investigation revealed that there was a significant decrease in the operative incidence in labors lasting 30

to 36 hours, as shown in Fig. 7, and a comparable significant increase as revealed in Fig. 8 in the operative incidence in the group with labors lasting 37 to 48 hours. Fig. 9 illustrates a smaller increase in the number of operative deliveries in labors lasting 49 to 60 hours, but no in-

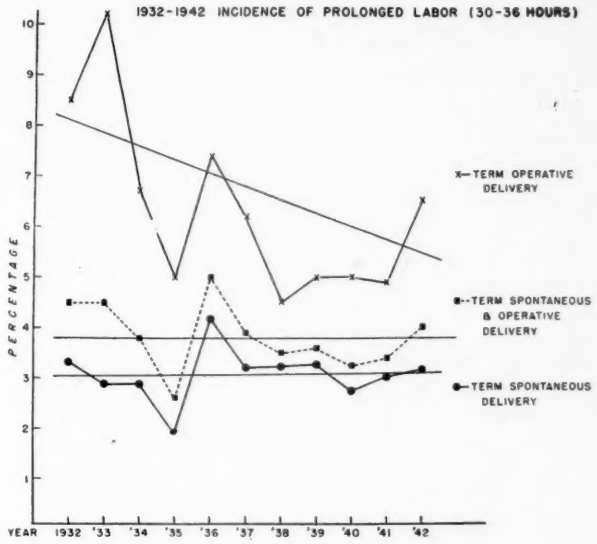

Fig. 7.

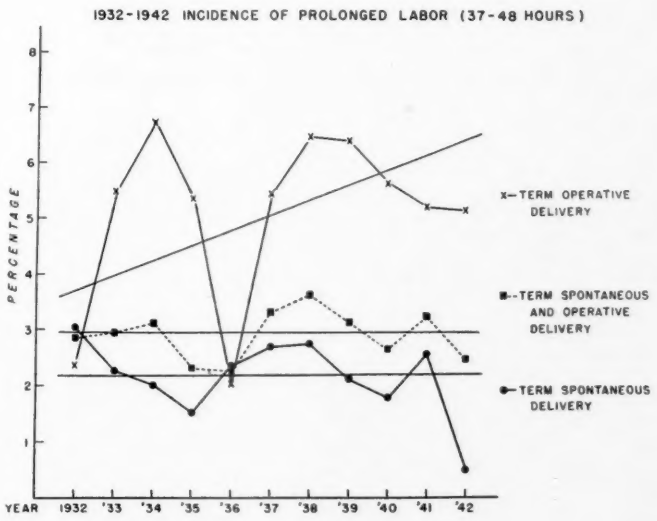

Fig. 8.

crease in the labors lasting longer than 60 hours, as is shown in Fig. 10. The interpretation of this information is quite interesting and would seem to suggest that we have tended to interfere less frequently in labors lasting 30 to 36 hours and somewhat more frequently in labors lasting 37 to 60 hours. What this probably means in actual practice is that

in the more recent years we have not interfered as frequently in the labors of 30 to 36 hours where possibly the cervix was incompletely dilated, but have awaited full or more complete dilatation of the cervix, and they were then included in the group whose labors lasted from 37 to 60 hours.

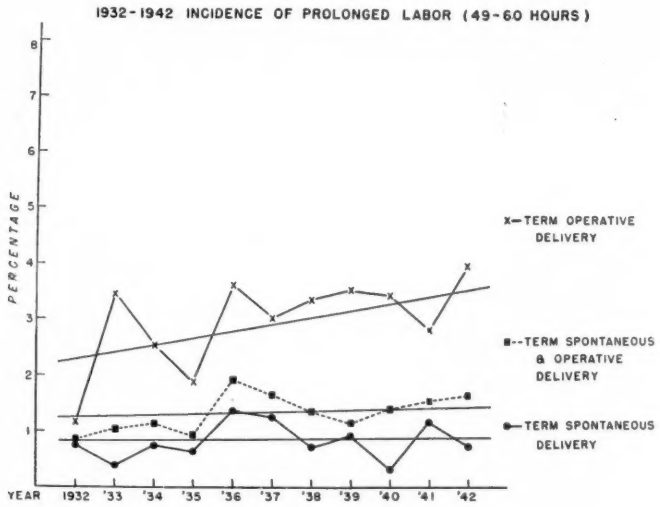

Fig. 9.

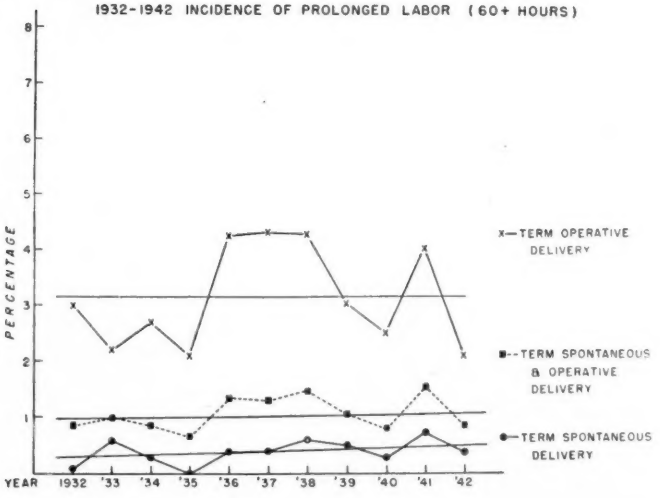

Fig. 10.

In general, it may be said as a result of studies of these data that prolonged labor per se exerts a deleterious effect on both the maternal and fetal organisms and the severity of this deleterious effect increased progressively with the duration of labor. Where labor is terminated operatively there is a superimposed effect caused by the procedure in question.

In the second section of this contribution we will attempt to find an explanation for the increased infantile mortality that is caused by the prolonged labor itself. All other factors may be wholly or partially excluded in this study. Prior to undertaking this investigation in 1934, we were impressed with the fact that during a prolonged labor the infant often died in utero where there was no serious disproportion or other traumatic factor that might explain the death of the baby. In fact, in many instances the syndrome of premature rupture of the membranes and desultory labor, followed by clinical evidence of infection in the vaginal discharge and in many instances an accelerated pulse rate and an elevated temperature appeared to be characteristic of this condition. Under these circumstances we have frequently observed the death of the fetus in utero and oftentimes the autopsy failed to reveal findings that would adequately explain the fetal death. It was for this reason that we decided to take blood cultures immediately following the delivery of stillborn infants. The technique employed consisted in preparation of the skin over the precordium with iodine and alcohol and a sterile needle attached to a 5 c.c. syringe was then inserted directly into the heart. It is usually possible to obtain blood or plasma in this manner for culture. The blood was inoculated into different media and incubated under both aerobic and anaerobic conditions. The subsequent identification of the organism present was carried out by recognized bacteriologic procedures.

We have employed the same technique in studying the blood obtained from babies that died following labors where there was an obvious cause for death, such as intracranial hemorrhage, congenital abnormality, asphyxia, et cetera, and this material serves as a control. It will not be detailed at this time other than to state that in the great majority of instances the cultures were sterile. We investigated a total of 140 babies where the blood cultures were negative and all available data indicate that there was usually some perfectly obvious cause of death. There was a total of 225 babies so studied and the blood cultures were positive for one or more organisms in 85 instances. Tables I to XI have reference only to this latter group.

Table I shows that of the 85 who had positive blood cultures, 83 of the infants were stillborn or deadborn, one was a neonatal death that occurred approximately 24 hours after delivery, and the other infant remained alive. A culture from this particular baby was obtained from the cord blood. In the second section of this table, it is seen that a definite intra-partum fever was present during the course of labor in 59 of the 85 mothers. In 26 there was no fever, but in many instances the vaginal secretions gave definite evidence of an intraovular intra-partum infection. The seriousness of this complication is illustrated by the fact

TABLE I

1. Total number of babies with positive blood culture		85
	83 stillborn or deadborn	
	1 neonatal death	
	1 living	
2. Number of mothers with intra-partum fever:		
	26 none	
	3 low grade	
	56 febrile	
3. Maternal deaths		3

that there were three maternal deaths in this group of patients, two of them caused solely by fulminating infections, while in the third patient the cause of death was not so clear. In Table II it is seen that the fetal heart stopped just prior to, during, or immediately following delivery on 20 occasions. In 16 instances the fetal heart stopped during pregnancy at various periods of time prior to the onset of labor, while in 47 instances the fetal heart stopped during the course of labor without apparent cause at an average time of seventeen and one-half hours before delivery.

TABLE II

a. Number fetal heart stopped during delivery	20
b. Number fetal heart stopped during pregnancy, i.e., before onset of labor	16
c. Fetal heart stopped an average of 17½ hours before delivery where the fetal heart was lost during labor	47

The question immediately arises as to whether there were any clinical factors that might explain these deaths. Table III illustrates such factors as might have been considered, but it is apparent that they were not necessarily related to the actual cause of the death of the baby. It is significant to note that no clinical cause could be found in 74 cases. It is quite possible that in the two instances of placenta previa and premature separation these factors may have been entirely, or at least

TABLE III. SUGGESTED CLINICAL CAUSES OF DEATH

	NO. CASES	PER CENT
Cord around neck	4	4.7
Toxemia	2	2.4
Placenta previa	2	2.4
Premature separation of placenta	2	2.4
*Unknown	74	87.1
Living	1	1.2
Total	85	

*Intrapartum infection.

in part, responsible for the death of four babies. Table IV illustrates the method of delivery in this group of infants, and it is seen that approximately one-third delivered spontaneously, while in two-thirds operative measures were employed. Approximately 25 per cent of the total group were delivered by means of forceps, 15 per cent by craniotomy, and 17 per cent by breech extraction. It must be recalled at this time, as was illustrated in Table II, that in 63 of the 85 babies involved the fetal heart had stopped prior to the actual delivery. Table V illus-

TABLE IV. METHOD OF DELIVERY

	NO. CASES	PER CENT
Spontaneous	30	35.3
Operative	55	64.7
Forceps	21	24.7
Craniotomy (vertex)	13	15.3
Voorhees bag, spont.	4	4.7
Breech extraction (preceded by bag, 6)	15	17.6
Version and extraction	1	1.2
Cesarean section (Porro)	1	1.2

trates the duration of labor and the length of time the membranes were ruptured prior to the time of delivery. It may be seen that in 26 cases the duration of labor was not prolonged, and in most instances in this group the fetal heart stopped prior to the onset of labor. On the other hand, in 58 cases, labor was of more than 30 hours' duration, the average being a little over 62 hours, and the membranes were ruptured an average of 63 hours before delivery. The table also shows the number of instances where the labor was 30 to 36 hours, 37 to 48 hours, 49 to 60, and 60 plus hours.

TABLE V. DURATION OF LABOR AND LENGTH OF TIME MEMBRANES RUPTURED PRIOR TO DELIVERY

NO. OF CASES	DURATION OF LABOR IN HOURS	AVERAGE LENGTH OF LABOR	AVERAGE NO. HOURS MEMBRANES RUPTURED PRIOR TO DELIVERY
26	0-29	12.7	28.4
10	30-36	33.2	53.7
10	37-48	40.6	46.8
13	49-60	54.5	56.5
25	60+	86.7	76.8
58	30+	62.3	63.0
84	0-60+	47.0	52.8

Table VI illustrates the autopsy findings. It is seen that an autopsy was performed on all infants excepting 12. As was previously shown in Table II, the fetal heart stopped during pregnancy and prior to labor in 16 cases, and an average of 17½ hours before delivery on 47 occasions. Accordingly, the number of babies that were hopelessly macerated as far as the possibility of studying cellular pathology is concerned is relatively large. In approximately one-third of these babies no finding

TABLE VI. AUTOPSY FINDINGS

	NO. CASES	PER CENT
Maceration	28	32.9
Not macerated, no cause	4	4.7
Petechial hemorrhages	22	25.9
Pneumonia	13	15.3
Aspirated material in lungs	2	2.4
*Other	4	4.7
No autopsy	12	14.2
Total	85	

*Prematurity, congenital abnormality, etc.

other than maceration could be determined. It may have been in many of these instances that some significant change might have been discovered had it not been for the extensive maceration. In a considerable number of infants that showed petechial hemorrhage, fairly extensive maceration was also present. Furthermore, this condition is frequently encountered where babies die from asphyxia. The number of infants that actually had a definite pneumonitis was only 15 per cent, although it is quite possible that the incidence of this finding might have been considerably raised had it not been for the extensive maceration that was so frequently present. Interestingly enough, there was only one congenital abnormality that might have been responsible for the fetal death in the entire group.

The results of the histologic examination of the placenta is illustrated in Table VII. In over half of the placentas there was definite evidence of an acute and active infection. The placenta was normal in 17 per cent of instances, and in 12 per cent maceration was quite extensive. In five cases no sections were studied microscopically. The other findings in this table appear to have no practical bearing on the subject in

TABLE VII. HISTOLOGIC EXAMINATION OF PLACENTA

	NUMBER	PER CENT
Placentitis	44	51.76
Normal	15	17.53
Maceration	10	11.65
No section	5	5.88
Degeneration	5	5.88
Retroplacental hematoma	2	2.4
Other (prematurity, syphilis, etc.)	4	4.7
Total	85	

question. Table VIII illustrates the results of cultures, and it is seen that in 66 instances a single organism only was recovered from the blood of the infant. The predominant organism was an anaerobic streptococcus. In 19 instances more than one organism was isolated, and again, the frequency of the finding of anaerobic streptococci is apparent. It is important to note that a careful study of all of these organisms reveals their similarity to strains that may be isolated from the vagina at the onset of, or during, labor. The important exceptions are the presence of the colon bacillus, *Staphylococcus aureus, H. influenza,* and *Bacillus proteus.* An analysis of the circumstances where these organisms were recovered revealed either repeated vaginal examinations,

TABLE VIII. RESULTS OF CULTURES OF HEART BLOOD

	CASES	PER CENT
Single Infection		
Anaerobic streptococci	25	29.4
Diphtheroids, aerobic + anaerobic	9	10.6
Streptococcus viridans	8	9.4
Aerobic nonhemolytic streptococcus	7	8.1
Staph. albus	6	7.1
B. coli	5	5.9
Hemolytic streptococcus (alpha prime)	3	3.5
Anaerobic staph.	2	2.4
Staph. aureus	1	1.2
	66	
Mixed Infection		
Anaerobic strept. + *B. coli*	3	3.5
Anaerobic strept. + diphtheroids	3	3.5
Anaerobic strept. + *B. coli* + *S. albus*	2	2.4
Anaerobic strept. + *Strept. viridans*	2	2.4
Other	9	10.6
(combinations of two or more of the following organisms: Aerobic nonhemolytic strept., *B. proteus,* diphtheroids, *Strept. viridans,* anaerobic strept., unidentified gram-negative bacillus, *S. albus, H. influenza, B. coli,* anaerobic staphylococcus)	19	

difficult operative procedures or maternal systemic infections that readily account for the presence of these organisms in the blood of the in-

TABLE IX. RESULTS OF CULTURES OF HEART BLOOD INCIDENCE OF INDIVIDUAL ORGANISMS

	NO.	PER CENT
Anaerobic streptococci	41	48.2
Diphtheroids	13	15.3
Streptococcus viridans	13	15.3
Staph. albus	11	12.9
Aerobic nonhemolytic streptococcus	9	10.6
B. coli	11	12.9
Anaerobic staphylococci	3	3.5
Hemolytic streptococcus	3	3.5
Anaerobic gram-negative bacilli	2	2.4
H. influenzae	1	1.2
Staph. aureus	1	1.2

fant. Table IX shows the frequency with which individual organisms were found. The percentage incidence in this group will considerably exceed 100, because, as was illustrated in Table VIII, two or more organisms were isolated on 19 occasions. The data indicate that the anaerobic streptococcus is by far the most important organism concerned. It is our belief that in the circumstances under review these organisms are all potentially pathogenic with the possible exception of the *Staphylococcus albus*. It was recovered alone in culture on only six occasions, and accordingly, it is our impression that the great majority of these babies actually had a pathogenic organism present in their blood at the time of delivery.

In a considerable number of instances (47) specimens of uterine lochia obtained post partum were studied bacteriologically and Table X

TABLE X. ORGANISMS FOUND IN BOTH CULTURES, LOCHIA AND HEART BLOOD

	NO.
Anaerobic streptococcus	20
Strept. viridans	9
Aerobic nonhemolytic streptococcus	8
B. coli	5
Alpha prime streptococcus (hemolytic)	3
Anaerobic staphylococcus	2
H. influenza	1
Staph. albus	1

illustrates the organisms that were found in both cultures, namely, the heart blood of the child and the uterine lochia. Again, the anaerobic streptococcus plays the most significant role. The importance of the lower genital tract as a source of infection, namely, in causing first an intra-partum maternal infection and then an infection of the baby is obvious. Table XI illustrates the number of times there was a definite correlation of one or more organisms found in the heart blood and the

TABLE XI. CORRELATION OF ONE OR MORE ORGANISMS FOUND IN HEART BLOOD AND THE UTERINE LOCHIA

Uterine lochia not studied bacteriologically		38
Cases where uterine lochia was studied		47
Correlation	40	
No correlation	7	

uterine lochia. In 38 instances it was found that the uterine lochia was not studied bacteriologically and, accordingly, no correlation was possible. In the remaining 47 cases where a correlation was possible, it is seen to be present in 40 occasions and absent in only seven.

Discussion

Infantile mortality has shown no appreciable or significant reduction during the past ten years, such as has been accomplished in the maternal mortality rate throughout this country. The uncorrected infantile mortality rate in our clinic remains between 3 and 4 per cent. Prolonged labor, occurring in 9 per cent of our patients, plays a major role in this high death rate.

When prolonged labor terminates spontaneously, the incidence of puerperal infection is 9.01, 10.59, 13.11, and 11.70 per cent for the periods of duration of prolonged labor of 30 to 36, 37 to 48, 49 to 60, and 61 or more hours, respectively. The comparable incidences of morbidity for these periods are 11.70, 13.90, 15.30, and 14.89 per cent, respectively. On the other hand, when prolonged labor is terminated by operative means, the incidence of both puerperal infection and morbidity is doubled or trebled, the former being 20.57, 22.65, 32.82, and 43.00 per cent and the latter 23.43, 24.47, 35.90, and 47.50 per cent for each of the four periods of duration described above, respectively.

For these four periods of duration of prolonged labor, the infantile mortality rate in spontaneous delivery is 2.05, 2.86, 5.46, and 8.36 per cent, respectively; while in operative delivery the rate is 8.33, 12.68, 16.92, and 29.50 per cent, respectively.

The incidence of forceps delivery in prolonged labor is 35.51 per cent (compared to our total incidence of 14.94 per cent) with an infantile mortality of 10.88 per cent as compared with an infantile mortality rate in forceps delivery for the whole Clinic of 4.85 per cent. Breech extraction and cesarean section reveal equally unsatisfactory infantile mortality rates in the prolonged labor group, the former with 22.46 per cent (Clinic 13.47 per cent) and the latter 12.90 per cent (Clinic 9.8 per cent). An analysis of these unsatisfactory fetal results on the basis of the four periods of duration of prolonged labor (30-36, 37-48, 49-60, and 61 plus hours) shows that in forceps delivery the infantile death rate is 5.59, 9.23, 10.69, and 23.89 per cent, while in breech extraction the rate is 16.66, 21.56, 33.33, and 33.33 per cent for each of the periods, respectively.

A further analysis of our results in prolonged labor showed an appreciable decrease in the infantile mortality following operative delivery. The only explanation for this reduction appears to be the fact that we have tended to interfere less frequently in labors of 30 to 36 hours and slightly more frequently in those lasting 37 to 60 hours.

It is our feeling that the evidence presented strongly suggests the fact that organisms present in the vagina at the onset of labor become

invasive and pathogenic during the course of labor. Various reasons have been advanced by different investigators to explain this phenomenon. It is not our purpose, however, at this time to discuss this particular question. If other organisms are introduced into the vagina during the course of labor they also may play a rôle in the development of intra-partum infection. The rapidity with which this infection develops is greatly enhanced by early rupture of the membranes. At the same time, these studies indicate that the apparent intact membranes do not constitute an impassable barrier to such microorganisms as have

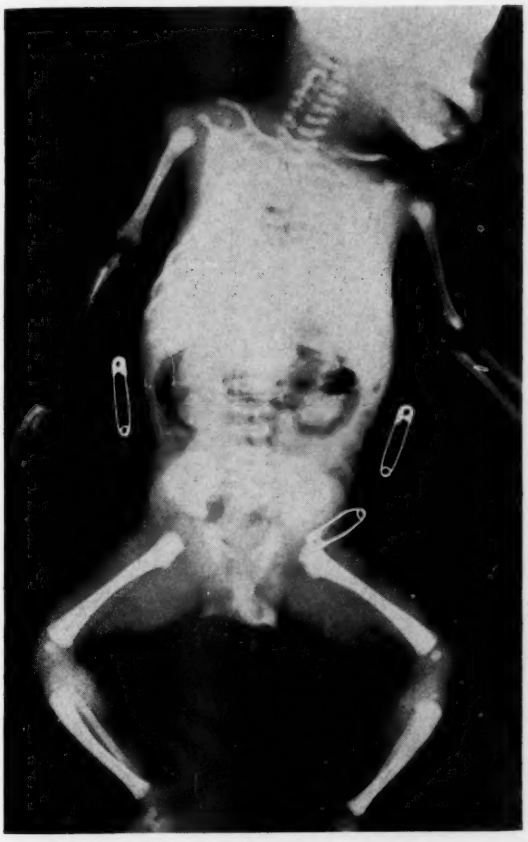

Fig. 11.

been discussed. The most frequent site of infection is first intraovular, then the fetal membranes, the placenta, and the maternal tissues. It appears probable that if the placenta is situated high in the fundus that it is most likely to be involved late in comparison with the placenta that is situated nearer the cervix. It would appear quite possible for these organisms to pass from the maternal portion of the placenta to the fetal circulation and thence to the baby. Another apparently common method of fetal invasion is the direct extension through the respiratory passages to the lungs where a pneumonitis develops. A third and long recognized

possible mechanism is illustrated in several of our patients where there was a maternal blood stream infection. Such an infection may extend from the maternal to the fetal blood through the medium of the placenta.

An analysis of the autopsy findings reveals that there was definite pathologic evidence of infection present in only about one-fifth of these babies. We are not prepared to state that the septicemia that we have reported or the mere presence of organisms in the blood stream was definitely responsible for the death of the baby. However, on the other hand, if there was no obvious clinical cause of death and a definite bacteriemia was present, it would seem to suggest that the infection was at least the only possible etiologic factor known. Negative autopsy findings, especially in macerated infants, do not preclude the possibility of an extensive infection, as is illustrated in the following two cases.

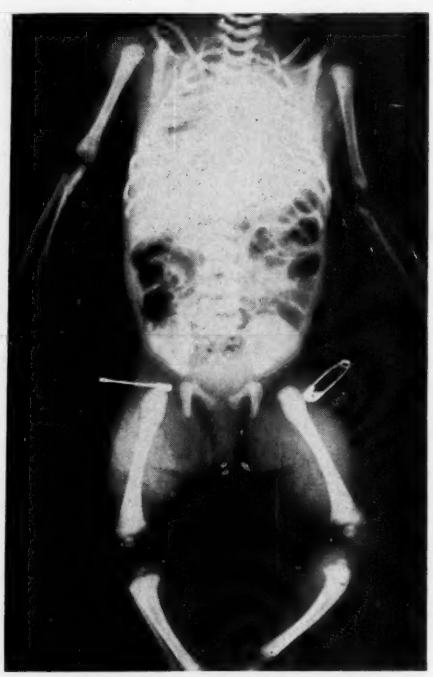

Fig. 12.

Fig. 11 is from an untouched roentgenogram taken shortly after the birth of a baby delivered following a labor of 105 hours where the membranes had ruptured prematurely. The fetal heart stopped twenty-four hours before delivery which was effected by an easy low forceps. The culture of the heart blood revealed an anaerobic nonhemolytic streptococcus and diphtheroids. The uterine lochia contained an anaerobic nonhemolytic streptococcus and *B. coli.* No cause of death or *significant* pathology was found at autopsy. The gas present in the intestines, heart, abdominal aorta, and in the large vessels of the extremities has undoubtedly been caused by the metabolism of the organisms present.

Fig. 12 was made from the film of a baby dying nine hours before delivery which terminated spontaneously following a sixty-five-hour labor where the membranes ruptured prematurely. Both uterine lochia and heart blood revealed an anaerobic nonhemolytic streptococcus on culture. Again, the autopsy findings were not significant excepting for extensive maceration, while the film reveals gas in the lungs, intestines, and large vessels. The evidence here adduced, of course, does not necessarily mean that the infection was acquired before the death of the baby. All or some of the gas formation may have developed in utero after the death of the baby.

When one attempts to rationalize the management of obstetric patients from the point of view of obviating this unfortunate possibility, it at once becomes evident that the most important single factor is to prevent prolonged labor. Unfortunately, our foresight on this subject is at times worth but little, while often in retrospect we wish that our management had been different. We recognize that infection starts coincidentally with every labor, that the rapidity with which it develops is enhanced if the membranes are ruptured. In the great majority of instances labor is terminated prior to clinical evidence of infection. However, approximately 9 per cent of labors are prolonged; and as soon as this complication is encountered the development of clinical intrapartum infection becomes a real possibility, and the unfavorable effects will be encountered in babies with increasing frequency as the duration of labor is extended. Unfortunately, the means at our disposal of predicting a long labor are not very reliable. Again, our methods of improving the quality of labor and shortening its duration are often not very effective. Medicinal stimulation, such as castor oil and quinine, may be of some help. Physical stimulation, such as hot enemas, hot drinks, massage of the fundus, et cetera, are at times helpful, but cannot always be relied upon. The use of oxytocics is usually not indicated. At times, good results have followed the employment of intranasal pituitary extract following the so-called medical induction, and possibly on rare occasions the same may be said of very small doses of the same drug injected intramuscularly where the patient is under the closest observation and supervision.

Another approach to this problem that certainly should be considered at this time would be the use of a sulfonamide drug during the course of prolonged labors. We have had the opportunity of studying some patients in this manner and, in general, our experience indicates that the drug is of little or no value if it is not employed until after the development of fever and a purulent vaginal discharge. On the other hand, we have observed a beneficial effect where the medication was given somewhat earlier in prolonged labors. It is necessary in such instances to make every effort to improve the quality of labor at the same time. The sulfonamide drug that we prefer at this time is sulfadiazine. It is imperative in patients who are receiving this compound that an adequate urinary output be maintained. Accordingly, it becomes most important

that accurate records of the urinary output be kept, and intravenous glucose should be employed if it is not adequate. An optimum output should be at least 50 and preferably 75 c.c. per hour. Recent evidence indicates that crystallization of the drug in the urinary tract may be avoided if sodium bicarbonate in large doses (4 Gm. every 4 hours) is administered at the same time. At times this latter medication may be contraindicated because of a toxemia and associated water retention.

It is our feeling that these considerations should be carefully evaluated before prematurely terminating a prolonged labor. It is difficult to know in any given case when infection is present in the baby. For reasons poorly understood fetal death may occur in some instances after 40 hours of labor, while in others it does not occur after the lapse of 100 hours under comparable conditions. Again, while the fetal death may be preceded by a rapid rate of the baby's heart, this is not always the case and the death in utero occurs without any prodromal signs. Radical procedures aimed at delivery before complete dilatation of the cervix so often result in extensive maternal trauma, causing blood loss and shock, spreading infection, and may in no way be compensated for by the birth of a living baby, because so often the babies are already infected and may die at the time of delivery or shortly thereafter. It may be that the presence of the fetal bacteriemia explains the long recognized clinical fact that babies delivered following prolonged labor withstand any operative procedure very poorly. This all implies that if at all possible such labors should be terminated spontaneously. There will be many instances when this is impossible, but it would appear that we are not justified in undertaking relatively radical operative procedures where the main indication is the hope of obtaining a living baby. By adherence to this principle we will continue to lose some babies as a result of intra-partum infection and the subsequent fetal bacteriemia, but we will not traumatize the mother and produce a state of shock and end up with a stillborn infant. We do not imply by these statements that there are not occasions when expert obstetric judgment and skill may be applied and labor terminated operatively with a happy outcome for both the mother and infant.

Conclusions

1. The incidence of puerperal infection, total morbidity, maternal and infantile mortality increases progressively with the duration of labor, and in prolonged labor all are much increased when labor is terminated by operative means as compared to spontaneous delivery.

2. The incidence of prolonged labor has remained unchanged during the past ten years in the New York Lying-in Hospital.

3. Infantile mortality following prolonged labor has decreased steadily during the past decade. This decrease has been effected largely through a decreased rate following operative delivery.

4. The incidence of operative delivery following labor of 30 to 36 hours has decreased, while there has been an increase in operative delivery following labor of 37 to 60 hours. There has been no change in labors lasting more than 60 hours.

5. A fetal bacteriemia was found in 85 stillborn infants, most of whom were born following prolonged labor with intrapartum infection.

6. In the majority of these infants there was no pathologic lesion to explain the death, and the idea is advanced that infection may have been responsible.

7. The origin of the intra-partum infection was for the most part autogenous (from the maternal genital tract) and subsequently extended to the baby by various routes.

8. The anaerobic streptococcus (including facultative strains) was the most common organism found in the infant.

9. Efforts should be directed toward improving the character of contractions in desultory labors with a view to shortening the total duration of labor.

10. In general, operative procedures aimed at delivery following prolonged labor give poor results. The best results, on the other hand, follow spontaneous delivery.

11. Our recent but, as yet, limited experience indicates that sulfadiazine may prevent, to some extent at least, the development of intrapartum infection if employed relatively early in prolonged labor. On the other hand, if it is employed after the frank development of intrapartum infection, it has little or no therapeutic effect.

A FURTHER CONTRIBUTION TO THE SYNDROME OF FIBROMA OF THE OVARY WITH FLUID IN THE ABDOMEN AND CHEST, MEIGS' SYNDROME*

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IN 1937 in the AMERICAN JOURNAL OF OBSTETRICS AND GYNECOLOGY, Meigs and Cass[1] presented the histories of four patients who had ascites and hydrothorax associated with fibroma of the ovary and relieved of their serous fluids by removal of the tumor. No reasons were found that adequately explained the phenomenon. In the years following the first presentation of this syndrome, other cases were reported and brought to the authors' attention, so that in 1939 in the *Annals of Surgery*[2] 15 cases were summarized. Later, in 1940, in an

*Presented, by invitation, at a meeting of the New York Obstetrical Society, January 12, 1943.

article in Frank Howard Lahey's *Birthday Volume,*[3] the total was brought to 18. The present report increases the number of authentic cases to 27. It is obvious therefore that this syndrome is of considerable importance, for some patients have died without proper surgical relief and some who were doomed because of considered inoperable malignancy are now well. In 1941 the senior author (J. V. M.) operated upon two patients and his associate, Langdon Parsons, operated upon another (Ritvo's[4]) on his service at the Pondville Hospital. Thus the occurrence of three lesions of this type in one year demonstrates effectively that it must always be considered in a differential diagnosis of abdominal and chest fluid. J. V. Breen and T. H. Nelligan[40] have kindly allowed us to include in the synopses the history of their patient operated upon in the "House of Mercy Hospital," Pittsfield, Mass., on Nov. 15, 1940, and not as yet reported. In 1937 Muriel B. McIlrath[5, 6] stimulated further investigation into the literature which resulted in the addition of two cases to the total, and again in June, 1942, she located a report by Lawson Tait in which he advocated exploring patients with abdominal and chest fluid for he considered that this combination did not always mean cancer. Thus the old adage is proved that "there is nothing new under the sun." Lawson Tait's[7] discussion, somewhat abbreviated, is quoted below:

"L. T., single, aged 36, was sent to me by Dr. Brown of Tintern in January, 1890, with a large abdominal swelling. . . . About June, 1889, her abdomen was noticed to be enlarged. This steadily increased, very rapidly during December, 1889.

"For a month before admission she had severe cough, shortness of breath, and night sweats, with profuse expectoration of much black-colored stuff.

"Condition on admission (January, 1890)—body generally emaciated, abdomen greatly enlarged. She breathed rapidly and with difficulty. On examining the chest the left side was absolutely dull nearly up to the clavicle. There was no vocal fremitus or vocal resonance, the intercostal spaces were increased and bulged, the left side of the chest moved but slightly during respiration, and the heart was displaced to the right. There was evident hydrothorax of the left side.

"On examining the abdomen . . . there was all the physical signs of ascitic effusion free in the peritoneal cavity. In addition there could be felt on deep pressure through the fluid a large rounded solid tumor, apparently moored in the pelvis and floating freely in the ascitic fluid. As the breathing was much distressed the left pleural cavity was aspirated, and ninety-five ounces of blood-stained serum removed. A few days after the tapping of the left side fluid was discovered in the right pleura and was similarly removed. It contained a quantity of blood. The diagnosis of malignant disease of the peritoneum with secondary infection of the pleural surfaces was made. I declined to operate on the abdominal tumor, and the patient returned home to die.

"About a fortnight after returning home her left pleura was again tapped, and eighty ounces of pale yellowish fluid removed. In February, 1890 the abdomen was tapped, and eleven quarts of pale yellow thin ascitic fluid removed. From this time until February, 1891 her

abdomen was tapped over thirty times, from eight to fourteen quarts of thin clear yellowish fluid being removed at each operation. She was last tapped on February 28, 1891 when eleven and a half quarts were removed. The pleural effusions did not recur. The patient was readmitted on March 4, 1891; she was then in much better health. She had no pulmonary symptoms, and she was not so emaciated. The pleural effusion had not reappeared since the last thoracentesis in January, 1890.

"On examination there was an impaired percussion note over the base of the left lung behind, and distant breath-sounds. The abdomen was distended with free ascitic fluid, floating in which could be felt the solid tumor before described.

"There was no edema of the legs and no albumin in the urine.

"Operation on March 5th, 1891—I opened the abdomen by short vertical incision in the midline. As soon as the peritoneal cavity was reached a large quantity of ascitic fluid escaped. The tumor was now discovered to be a large solid growth of the right ovary. It was quite free from adhesions save to the ovary of the other side. The tumor was delivered through the opening, and the pedicle transfixed and tied. The ovary of the other side was so adherent that it was removed. The tumor was now cut away, a glass drainage-tube inserted, and the wound closed. About the fifteenth day her evening temperature began to rise, and she had pain in the back and pelvis. On examination a tense rounded fluctuating swelling was discovered behind the uterus. On the twentieth day this was aspirated per vaginam, and twelve ounces of thick offensive grumous pus removed. It was aspirated again on the twenty-sixth day when five ounces of pus were removed. Three days later the pus again accumulated. This time, however, it burst into the vagina spontaneously, and continued to discharge for about a week. After this her recovery was uninterrupted but slow.

"The tumor weighed 2 pounds 2 ounces. It was nearly globular in form and quite solid. Attached to it were the ovary of the other side and the Fallopian tube of its own side. Microscopic examination showed it to be a fibroma. On its free surface were a few small cysts containing clear fluid.

"The lesion in this case is, in my opinion, a very valuable indication that no set of conditions in the abdomen, however apparently unfavorable, are sufficient to justify us in an absolutely unfavorable condemnation in any particular case. Looking back upon my experience of pleural effusion as complicated by abdominal disease, which I have said probably gives the somewhat insignificant number of twenty cases out of more than three thousand, I think that probably my general impression that it is a very fatal complication, especially when the fluid is of a bloody character is correct; and if half of the cases had been submitted to abdominal section, simply for the purpose of exploration and removing the bulk of fluid, the likelihood is not great that permanent benefit would have accrued in many of them; but if one of the lives had been saved by the discovery of a mistake, I think it would have quite justified the performance of the incision in all the rest for under such circumstances the mere opening of the abdomen has risk very little, if any, greater than the process of tapping, which has to be employed for the purpose of giving the patient relief. Tapping, however, has the disadvantage that it leaves the condition of diagnosis quite as imperfect as it was before the operation, and I have never in a single instance seen anything like a curative effect from the

process of tapping in the abdomen. Even in the successful case I have given in detail, tapping of the pleura did not seem to have the controlling influence of preventing further secretion; whilst in the abdomen it has no curative influence at all, having had to be repeated over thirty times. The striking results obtained in this case by the correction of my initial mistake have gone a long way to confirm me in the advisability of extending the principles of exploratory and confirmatory incisions in the abdominal disease to an almost universal application."

The senior author's new cases and those reported in the literature since his last presentation give the usual history and have the same physical findings, dyspnea, abdominal pain, and an abdominal tumor. New suggestions have been made to explain the fluid but nothing of any real value has been suggested. We do not know why there is fluid in the abdomen. In Case 25 (M. R.), the peritoneum in the region of the tumor was definitely inflamed and covered with fibrin so it is possible to assume that the fluid may be an inflammatory exudate, but this is not probable for other patients have not had any signs of inflammation in their peritoneal cavities. Twists of the tumors are rare, and adhesions are not common. It must be admitted that there is no explanation at the present time, but a letter from Dr. Thomas S. Cullen written after reading the 1940 article in Dr. Lahey's Volume is of great interest. Dr. Cullen has an explanation and to date it is more satisfactory than any other, but probably it will in the end be proved as not correct. Below is a slightly modified copy of his letter:

"I am not at all surprised that you have long wondered as to what caused the accumulation of the abdominal fluid, particularly as microscopic sections invariably show an intact surface to the tumor and no evidence whatever of small round cell or polymorphonuclear infiltration. One gathers no clue whatever from the microscopic examination.

"In the early 90's Dr. Osler saw a patient who had been all over Europe and who had been tapped many times. He sent her to Dr. Howard A. Kelly and he removed a fibroma of the ovary and also a large quantity of abdominal fluid.

"Early in 1897, when resident on Dr. Kelly's staff, I operated on a patient with a solid ovarian tumor and much free abdominal fluid.

"You will note that prior to my operation 23 gallons of fluid had been drawn off from the abdomen in a little over two months.

"The patient recovered after the removal of a fibroma of the ovary and there was no further edema or abdominal fluid.

"Nearly every case of fibroma of the ovary that I have seen has been accompanied by abdominal fluid."

On pages 30 to 38 in Kelly and Cullen's *Myomata of the Uterus,* there are described seven cases with considerable fluid in the abdomen. The authors believe that torsion of the pedicles of the tumors is responsible and they also mention that torsion of the loose pedicle of an ovarian fibroma is the reason for ascites in such cases. Partial rotation of the tumor with twisting of the vessels is responsible for fluid in the others. In this volume on page 32 is the report of a colored woman of 36 who had, in addition to abdominal fluid definite chest fluid; 1,550 c.c. of fluid had been withdrawn from the chest cavity before operation. The

patient was considered to have, in addition to her fibroids, mitral insufficiency and chronic nephritis. She recovered without complications. It is obvious, in our present knowledge, that the chest fluid was due to the same condition that caused the ascites.

Fluid in the abdomen accompanying fibroma of the ovary is a frequent finding and has been reported in all series reported in the literature. The removal of the tumor does stop the formation of the ascites; therefore there is a direct cause and effect. However, inflammation, twists, and omental adhesions are not common and therefore are probably not the only reasons for the presence of fluid. Lack of drainage of the right chest by the azygos vein was suggested in our first article as a cause of right pleural effusion, but fluid also has been found in the left chest and in both and thus does not seem an adequate explanation. In Case 19 the patient died and at autopsy the azygos veins were examined and found to be very large. Whether this indicates that they were busy with drainage or were interfered with is not at all clear.

The alarm reaction of Selye[10-12] as suggested in 1939 may still be considered as neither proved nor disproved. In this explanation, arguing from data on animals, repeated minor trauma to the peritoneum by the fibroma causes a resistance of tissues which later return to normal but after a period of months with continued trauma the resistance disappears, and then there appears a histamine toxicosis or anaphylactic shock plus accumulations of peritoneal and pleural transudate. In experimental work such an explanation in certain animals with shock and serous exudates is possible but to explain this syndrome on the basis of such experimental findings cannot be done.

Serum protein determinations have been found normal in a sufficient number of cases to rule out edema due to this cause as an explanation. It is true that some patients have edema of the legs and lower body but this was not always the case. There is insufficient evidence to explain gross chest and abdominal fluid by protein lack.

Cardiac and renal conditions may account for accumulations of fluid, but the patients here reported did not have cardiac or renal disease.

One of the most interesting phenomena observed in some cases is the tremendous accumulation of fluid in the chest with only small amounts in the abdomen. It is almost as if there were an attraction in the chest for the abdominal fluid. The fluid may accumulate overnight after the chest has been tapped, there being as much in the chest as on the day before. The amount of fluid may be very great and a great many tappings may have been carried out. Cachexia may appear, the patient being unable to keep up the supply of fluid, and dehydration and death may occur; yet the amount of fluid in the abdomen, the probable source of the fluid, may remain within limits easily compatible with life. The reverse may be true, as in Lawson Tait's case, but it is not so common.

Two patients operated upon in 1941 presented an opportunity to palpate the structure of the diaphragm, to collect fluids for investiga-

tion, and to show that particulate matter could pass from the abdominal fluid into the chest fluid. Case 24 was referred by Dr. H. H. Hamilton of Plymouth, Massachusetts with a diagnosis of Meigs's Syndrome. At operation a large opening was found in the diaphragm in front of the aorta connecting with the mediastinum. The question arose then whether or not fluid could pass from the abdomen into the right chest which contained fluid through this passage. A few days later one of the authors (J. V. M.) called upon Dr. William E. Ladd[13] of the Children's Hospital in Boston and asked if such an opening was possible. Dr. Ladd felt that a passage from the abdomen into the chest, a so-called pleuroperitoneal canal was a definite possibility but that it probably was not often compatible with adult life.

In an article written by Ladd and Gross,[14] in 1940, they say "The situations in the diaphragm where congenital hernia occurs are the left and right sides posteriorly, where the defect is due to a persistent pleuroperitoneal canal (the foramen of Bochdalek), the esophageal opening, or the substernal opening commonly referred to as the foramen of Morgagni, of these hernias that occurring in a persistent pleuroperitoneal canal is by far the commonest. The fact that the hernia through the esophageal hiatus is commonest in adult life is due to the high mortality in infancy of patients with a hernia through the pleuroperitoneal canal."

In other words it is not likely that pleuroperitoneal canals exist in adult life, therefore the combination of a fibroma of the ovary and a pleuroperitoneal canal could not be so common as the syndrome under discussion seems to be. Harrington,[15] in 1942, in discussing diaphragmatic hernia in children, lists 6 of 21 as being of the type of hiatus pleuroperitoneal; yet in a list of diaphragmatic hernias in adults in the same article he finds but two in 283. In other words this type of hernia with direct opening from the peritoneum to the pleural cavity is rare, most children with it having died until the more modern operations of Ladd and of Harrington. In discussing our problem with Dr. Richard Schatzki[16] of the roentgenologic department of the Massachusetts General Hospital he pointed out that Lambl[17] states that at an autopsy on a 33-year-old man he found absence of the diaphragm in small areas with viscera in the chest cavity. These were not true hernias as there was no peritoneal sac, but an opening through the diaphragm. In his patient there was also absence of the pericardium. It is possible therefore that a continuation of the peritoneal pleural opening without intervening hernial sac can occur. An autopsy of a patient with a pleuroperitoneal canal is described, and Ladd and Gross admit its possibilities, and Harrington has operated upon two adult patients with such an abnormal diaphragmatic development. It is clear, however, that the rarity of this condition of the diaphragm makes it very unlikely that in the 27 patients with ascites and fluid in the chest and a fibroma of the ovary that such an opening could be present. A chance to verify this possibility came with the next patient (Case 25) referred by Dr. E. D. Churchill and operated upon in the Baker Memorial Hospital of the Massachusetts General Hospital. At operation the diaphragm was carefully explored and no opening found. A small opening could not be ruled out by palpation of the diaphragm from a lower abdominal incision but certainly no opening of any considerable size existed.

During the preoperative investigation of Case 25, fluid was removed from the chest cavity and 600 c.c. of air introduced into the pleural

cavity. The patient was then placed on the tilt table in the x-ray department with the hope that air might be forced from the chest into the abdomen through a possible pleuroperitoneal canal or any other opening, but the x-ray report which follows shows that: "there was a large quantity of air in the right pleural cavity. There was considerable fluid remaining. The patient was tilted into Trendelenburg position so that the air in the pleural cavity came in contact with the diaphragm. She was then placed on each side and back, films being taken to show free air in the abdomen in each position. There was no free air in the abdomen. The gas bubble in the fundus of the stomach was in normal position. There was no evidence of hernia. By x-ray, therefore, as well as by palpation no evidence of a canal could be found in this patient. In Case 26, reported by Ritvo,[4] the patient was peritoneoscoped previous to operation and a good deal of air was pumped into the abdomen to a point of discomfort and dyspnea in an effort to demonstrate any passageway for air from the abdomen to the thorax. After the peritoneoscopy, the air pressure was released to make the patient comfortable and a good deal purposely left in the abdominal cavity. Immediate x-rays were taken to demonstrate the presence or absence of air in the thorax. The x-ray findings showed that "there is no evidence of fluid at this time. (It had been removed as far as possible by chest tap previously.) Following peritoneoscopy, there is a considerable amount of free air in the peritoneal cavity about one inch below each diaphragm. In the subsequent films taken later and on the following day, there was still a considerable amount of air. There is no air in the pleural base or in the mediastinum." In the latter two patients there probably was no opening between the chest and the abdomen. In Case 24 there was a hernia, but it is not probable that this opening was of the pleuroperitoneal type. It is apparent therefore that it is unlikely that abdominal fluid arrives in the chest by way of a "hole" in the diaphragm. It is not possible to rule out groups of small openings that might occur through the muscle bundles and various attachments of the diaphragm. It would seem if such were present that the experiments tried in Cases 25 and 26 would have shown air in the abdomen in one and air in the chest cavity in the other. Such findings were not present.

How then does the fluid find its way into the chest? In two patients (Cases 24 and 25), 2 c.c. of sterile *India ink* was injected in the abdomen, and chest taps performed later. In each instance the fluid in the chest showed the same concentration of India ink as in the abdomen. Concentrations were gauged grossly. Microscopic examination showed essentially the same number of carbon granules in the mononuclear cells of each fluid. That the India ink did not arrive in the pleural fluid by way of the blood stream was considered established by study of the blood shortly after injection of the abdomen with India ink. In the two patients (Case 25, Fig. 1 and Table I), the blood showed no evidence of India ink in the leucocytes on microscopic examination. This experiment is suggestive evidence that the abdominal fluid in these

TABLE I. (CASE 25) CARBON INJECTION

Chest fluid: Mononuclear cells loaded with carbon
Abdominal fluid: Mononuclear cells loaded with carbon
Blood (Buffy Coat): No carbon seen

patients arrives in the chest by the same pathway as the India ink, or vice versa. The probability is that the pathways are lymphatics, first through the interstices of the cells under the diaphragm, thence to the supradiaphragmatic lymphatics and thence into the chest.

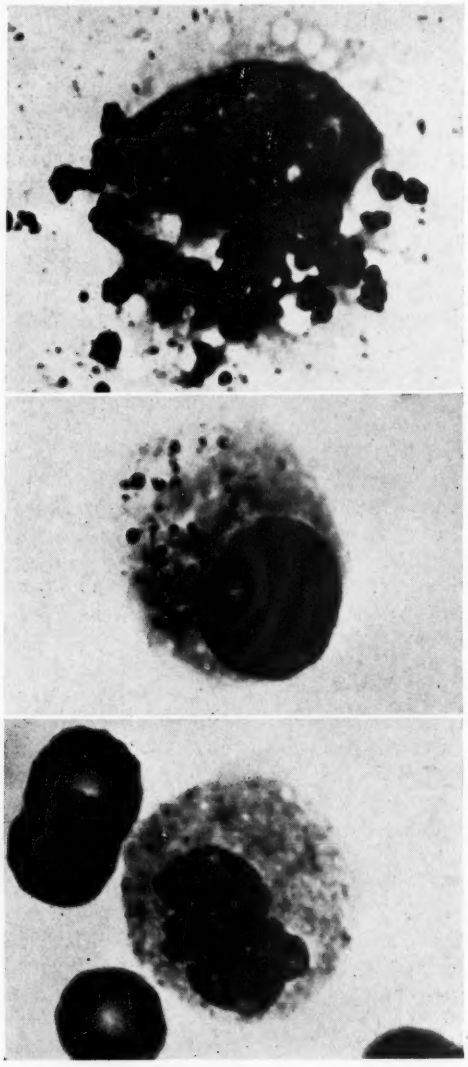

Fig. 1.—Case 24. Microphotographs of mononuclear cells from blood, chest, and abdominal fluids following the preoperative injection of India ink into the abdominal cavity. The cells from both chest and abdomen show phagocytosis of carbon particles; the cells from the blood do not.

Barring differential rates of absorption of components, if the two fluids come one from the other, they should be chemically identical. A comparison of the fluids of the chest and of the abdomen should provide corroborative evidence that the two fluids are in open communication. Fluids, therefore, taken by thoracentesis and from the abdomen at operation were compared as to total protein, and electrophoretic distribution of protein components, namely, albumin, alpha, beta, and gamma globulins, and fibrinogen. Such a comparison in two

patients (Case 24, Fig. 2 and Table II, and Case 25, Table III) shows that the two fluids are indistinguishable within the limits of the method.*

The identity of the fluids with respect to all aspects measured (protein concentration, protein distribution, India ink concentration) makes probable a fairly free communication between the fluids in chest and abdomen.

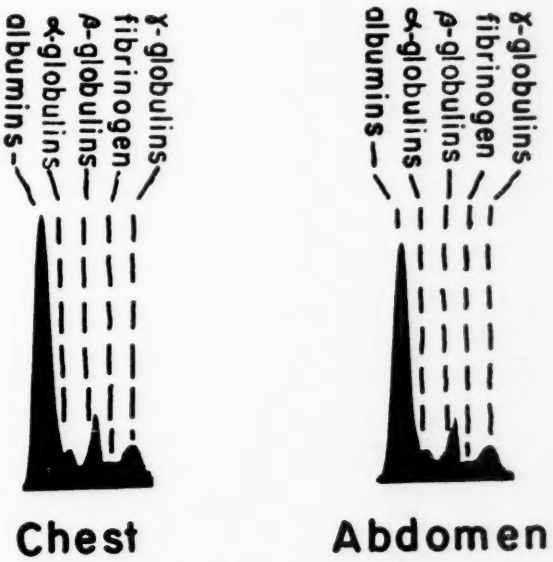

Fig. 2.—Case 24. The area of the skewed probability curve lying below each peak is a measure of the relative concentrations of the protein components noted above the peak. It will be seen that beyond a slight difference in total area (representing a difference in total protein concentrations at which the measurements were made) the patterns are essentially identical.

TABLE II. (CASE 24) ELECTROPHORETIC DISTRIBUTION OF PROTEINS IN CHEST AND ABDOMINAL FLUIDS

TOTAL PROTEIN	ABDOMEN 3.5 GM./%	CHEST 3.7 GM./%
Albumins	73.5%	73%
α-Globulins	5.5%	5%
β-Globulins	13.0%	13%
Fibrinogen	1.0%	2%
γ-Globulins	7.0%	7%

TABLE III. (CASE 25) ELECTROPHORETIC DISTRIBUTION OF PROTEINS IN CHEST AND ABDOMINAL FLUIDS

TOTAL PROTEIN	ABDOMEN 4.7 GM./%	CHEST 4.7 GM./%
Albumins	72.0%	72.0%
α-Globulins	4.5%	4.5%
β-Globulins	11.0%	10.5%
Fibrinogen	3.5%	4.0%
γ-Globulins	9.0%	9.0%

*The divergence between fibrogen concentrations lies below the limits of accuracy of planimetry in these schlieren diagrams.

TABLE IV. SYNOPSES OF 27 CASES OF MEIGS'S SYNDROME

CASE AND DATE	AUTHOR	AGE	STATUS	CHILDREN	CHIEF COMPLAINT	TUMOR	LOCATION OF EFFUSION IN THORAX	THORACENTESIS	ABDOMINAL PARACENTESIS	FLUID AT OPERATION
1. March, 1879	Cullingworth[25]	36	M	Yes	Metrorrhagia. Dyspnea. Collapse	Bilateral	Left	0	0	Died without operation. Autopsy
2. March, 1891	Tait[7]	36	S	?	Abdominal swelling	Right	Right and left	Repeated	30	Large quantity of ascitic fluid
3. April, 1901	M. G. H.[1]	42	S	None	Pain in right chest	Ovary	Right	4	1	Considerable straw-colored ascitic fluid
4. June, 1902	M. G. H.[1]	55	M	Yes	Pleurisy	Right	Right	5	0	6 to 8 quarts of ascitic fluid
5. Oct., 1908	M. G. H.[1]	38	M	Yes	Pain in shoulder, especially on left	Left	Right and left	7	4	Several quarts of ascitic fluid
6. July, 1917	Hoon[26]	36	M	Yes	Bloating of abdomen. Cough. Loss of strength	Ovary	Left	1	0	Marked ascites
7. Nov., 1920	Hoon[26]	53	M	None	Bloating. Pain between scapulae	Right	Right	3	1	Several liters of ascitic fluid
8. March, 1926	Leo[27]	64	?	?	Dyspnea. Pain in chest	Left	Right	Repeated	0	Large amount of ascitic fluid
9. April, 1928	de Rouville et al.[28]	58	M	Yes	Cough. Emaciation	Right	Left	1	9	1,000 c.c. ascitic fluid

10. Sept., 1930	Bomze and Kirshbaum[29]	37	M	Yes	Pain in abdomen. Lower abdominal mass	Left	Right and left	0	0	Free serous fluid
11. April, 1932	Salmon[24]	52	M	?	Abdominal mass. Cramps	Right	Right	3	0	500 c.c. ascitic fluid
12. Aug., 1934	M. G. H.[30]	52	S	None	Dyspnea. Change in bowel habits	Left	Right	Repeated	1	Large amount of yellow ascitic fluid
13. July, 1936	Miller[31]	60	S	None	Pressure. Weakness. Disability	Right	?	3	0	?
14. Aug., 1936	Weld[32]	55	?	?	Swelling of abdomen	Bilateral	Right	0	0	3,500 c.c. ascitic fluid
15. Sept., 1936	Weld[32]	50	M	?	Enlargement of abdomen	Right	Right	0	0	Blood-tinged ascitic fluid
16. Jan., 1937	Macomber[33]	33	S	None	Tumor in abdomen. Dyspnea	Left	Right	1	1	Two quarts of ascitic fluid
17. March, 1937	Rhoads and Terrell[34]	57	M	Yes	Shortness of breath. Fatigue	Right	Right	5	0	750 c.c. ascitic fluid
18. Nov., 1937	Bomze and Kirshbaum[29]	45	M	?	Lower abdominal mass. Bearing-down sensation. Backache. Edema of feet and ankles. Slight dyspnea. Left thoracic pain	Left	Left	0	0	Free serous fluid
19. July, 1939	Borg[35]	44	M	Yes	Pain in abdomen. Shortness of breath	Bilateral	Right and left	2	1	Died without operation. Fair degree of ascites at autopsy
20. Aug., 1939	Harris and Meyer[36]	67	M	Yes	Shortness of breath. Fatigue	Left	Right	1	1	200 c.c. ascitic fluid

TABLE IV—CONT'D

CASE AND DATE	AUTHOR	AGE	STATUS	CHILDREN	CHIEF COMPLAINT	TUMOR	LOCATION OF EFFUSION IN THORAX	THORACENTESIS	ABDOMINAL PARACENTESIS	FLUID AT OPERATION
21. Dec., 1939	Henderson[37]	42	?	?	Breathlessness	Bilateral	Right	4	0	Large amount of ascites
22. March, 1940	Lock and Collins[38]	31	M	Yes	Abdominal pain. Distention. Mass in abdomen	Left	Right	0	0	Four liters of clear fluid
23. March, 1941	Glass and Goldsmith[39]	73	?	?	Shortness of breath. Swelling of abdomen	Right	Right	1	0	400 c.c. straw-colored fluid
24. April, 1941	Meigs	66	M	None	Pleurisy. Backache. Asthma. Dyspnea	Left	Right	4	1	500 c.c. straw-colored fluid
25. June, 1941	Meigs	51	M	Yes	Cough. Dyspnea	Left	Right	3	0	500 c.c.
26. Dec., 1941	Ritvo[4]	57	?	?	Pressure in lower abdomen. Prolapse. Slight dyspnea	Right	Right	2	0	Two quarts
27. Nov. 8, 1940	Breen and Nelligan[40] (not reported in literature)	23	S	None	Swelling of abdomen. Frequency. Dyspnea	Right	Right	1	0	Large amount of straw-colored fluid

It should be noted that the chemical data alone do not lead to such a conclusion. They merely corroborate the implications of the rapid passage of particulate carbon from abdomen to chest. There is no a priori reason why chest and abdominal fluid, elaborated under similar pathologic conditions, whether comprising carcinoma or cardiac decompensation, be not essentially identical chemically. Indeed in a limited number of instances of cardiac insufficiency, simultaneous studies of fluids from peritoneum and pleura have demonstrated identity with respect to total proteins and electrophoretic distribution.[18]

It is evident that particulate matter, placed in the abdominal fluid of the two patients herein reported with a fibroma of the ovary and fluid in the chest arrives in some way, probably transdiaphragmatic, in the chest fluid.

The fact that air cannot follow the same route may well be merely an indication of the relatively small size of the communications: such that the pressures here involved were not sufficient to overcome the surface tension phenomena which in vitro can obstruct the free flow of air in a wet capillary tube.

The passage of particulate carbon is of considerable interest when considered with relevance to the mechanism of hydrothorax in conjunction with ascites in certain conditions other than Meigs' syndrome. Statistical considerations enhance this interest. For Meigs' syndrome is rare in comparison with ovarian fibromas with ascites alone.* So, likewise, is hydrothorax and ascites rare in comparison with Laennec's cirrhosis with ascites alone. It may be that hydrothorax is found in conjunction with ovarian fibroma or portal hypertension in those few patients who also have sufficient congenital mechanical communication between peritoneum and pleura. Extension of this hypothesis leads to investigation of the possibility of such communication in conditions where the basis of fluid in both cavities is more readily explicable, e.g., cardiac decompensation and metastatic carcinoma.

Initial experiments in this investigation have been completed. In two patients, one with carcinomatosis, the other with Laennec's cirrhosis; particulate carbon injected into the pleural fluid failed to attain the peritoneal fluid within twenty-four hours.

At first glance, this result might be taken to indicate that no communication exists in these instances. However, it should be noted that in two cases of Meigs' syndrome (Cases 24 and 25), only communication from abdomen to chest, not from chest to abdomen, has been demonstrated.

The possibility of a one-way communication is emphasized by the investigations of Lemon[19-21] and his associates on dogs. These workers found that particulate matter injected in the abdomen of the dog reached the diaphragmatic lymphatics, but particulate matter injected into the chest did not reach the inside of the abdomen.

They placed hydrokollag (a compound of graphite) in the peritoneal cavity of dogs and found the graphite particles in the supradiaphragmatic lymphatics and in the anterior mediastinal lymphatics. India ink as well as hydrokollag apparently penetrated the interstices of the cells of the subdiaphragmatic peritoneum and was picked up by the lymphatics and arrived in the lymphatics of the pleural diaphragm and later those of the mediastinum. Hydrokollag was also found in the retroperitoneal spaces about the spleen and kidneys, arriving there by

*Approximately 75 per cent or more ovarian fibromas are accompanied by ascites.

way of other lymph channels. Experimentally, then certain particulate matter can penetrate the diaphragm, but as experimental animals have no fluid in their chests, the question as to whether or not this material would enter a pleural effusion is not proved but is suggested.

Whether a truly one way communication can exist in man and to what extent the communication may be demonstrated in conditions other than Meigs' syndrome, will be discussed on completion of further studies.

No attempt has been made to include in this paper reports of cystadenomas, fibroids, or cancers with fluid in the chest as well as in the abdomen. A few reported cases are those of W. T. Dannreuther[22] whose patient, according to MacFee, ultimately died of cancer; a multilocular cystadenoma reported by MacFee;[23] a fibroid reported by Salmon,[24] and one case, mentioned in this paper, which is the only one of this type in *Myomata of the Uterus* by Kelly and Cullen.[9] There are not many reported as yet, and it is very possible that more will be. When they are, and when they constitute a large enough group, they should be included in the syndrome. It may be found that many benign pelvic tumors and certain malignant tumors without metastases in the chest may give rise to the same picture.

Conclusions

1. Two cases of Meigs' syndrome are reported wherein the fluid in the abdomen and chest were identical with respect to all aspects measured.

2. In these cases particulate carbon passed from abdominal to chest fluid quickly and easily.

3. Three important investigative problems emerge from Meigs's syndrome:

   a. The mechanism whereby ovarian fibromas give rise to abdominal fluid.
   b. The mechanism of the hydrothorax.
   c. The question as to whether similar mechanisms operate in instances of combined hydrothorax and ascites where the primary pathology is other than fibroma of the ovary.

4. Cullen, Kelly, and others, have shown that in lesions other than ovarian fibroma fluid may be present in the abdomen. Whether this fluid is similar to that found in patients with fibromas has not been proved, though it may be considered probable. In most cases of uterine fibroids with fluid there are adhesions of omentum to the tumor or twists of the pedicle which are not present in the fibromas reported here.

5. It remains for joint investigation by thoracic surgeons and others to demonstrate the presence of diaphragmatic perforations of small or large size, the presence of the rarely reported pleuroperitoneal tubes, and

to determine the direction and degree of penetrability of the diaphragmatic lymphatics.

6. The syndrome of ovarian fibroma with hydrothorax and ascites is of practical clinical significance. Further studies on patients thought to have cancer with metastases to the chest should be carried out.

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Discussion

DR. WILLIAM P. HEALY.—The most intriguing aspect of Dr. Meigs' paper is of course the question of how this fluid gets into the pleural cavity. I have had two cases, one benign and the other malignant, and in each instance there was fluid in the pleural cavity, in one case in the left and in the other in the right chest. In

the case with the malignant ovarian tumor there was no extension of the tumor to the chest, which, therefore, makes the problem similar to that of the nonmalignant cases.

My patient of benign ovarian tumor exhibiting this syndrome was on the service of both Mount Sinai Hospital and Memorial Hospital and the correct diagnosis was not made in either institution until I operated upon the patient. The case history of this patient follows:

G. B., a single Jewish woman of 48, was admitted to the Memorial Hospital on Nov. 29, 1931. She had been under observation in Mount Sinai Hospital for several weeks during September and October of that year. The menopause had taken place ten years previously. The present illness had began with swelling of abdomen four months prior to admission. This was soon accompanied by irregular abdominal pain and after a time, by shortness of breath. About two months previously the family doctor had made a diagnosis of abdominal tumor.

Physical examination disclosed a well-nourished female, who, however, appeared quite ill. There was dullness in the left chest posteriorly and evidence of pleural fluid. The abdomen was greatly distended and one could readily palpate a large, somewhat freely movable, ballottable mass which filled the pelvis and extended somewhat above the level of the umbilicus. The abdominal wall and ankles were somewhat edematous. Vaginal and rectal examinations disclosed no additional information.

A letter of inquiry which was sent to Mount Sinai Hospital elicited the following information: The patient had been in that hospital from Sept. 23 to Oct. 7, 1931. Two thousand cubic centimeters of amber-colored fluid was removed from the left pleural cavity after which x-ray of the chest showed an effusion of moderate size in the lower part of the left chest. The lungs showed no abnormality. No tumor cells were found in the laboratory examination of the pleural fluid.

The abdomen was distended by free fluid and an irregular tumor mass was noted extending from the umbilicus into the pelvis. Laboratory findings showed the following: sedimentation time, 10 minutes; hemoglobin, 66 per cent; blood Wassermann, negative; blood urea, 16. Gastrointestinal x-rays were negative except that the barium enema revealed an extracolonic mass occupying almost the entire left half of the pelvis, reaching to the level of the fourth lumbar vertebra. There was also an indication of another mass in the right half of the pelvis, displacing the colon upward but no intrinsic lesion of the colon.

The patient was considered inoperable and referred to Memorial Hospital for x-ray therapy. The final diagnosis was carcinomatosis peritonei.

When I saw the patient after her admission to the Memorial Hospital I first advised removal of the fluid from the peritoneal cavity so we could make a better examination. We removed 6,500 c.c. of clear, amber-colored fluid from the peritoneal cavity. A study of this fluid was reported as showing large mononuclear leucocytes, but no tumor cells could be identified. Following removal of the fluid I was able to identify two dense, hard tumor masses, on bimanual examination. Both these masses were mobile; one was about the size of a child's football and the other the size of a small orange.

On Dec. 1, 1931, I operated and found two large, readily removable fibromas of the ovary of the sizes noted. There was no evidence of intraperitoneal metastatic disease. A supracervical hysterectomy was done, removing the tumor masses with the uterus.

The pathologic report was: Left ovary absent and replaced by a large encapsulated, nodular tumor measuring 17 by 15 by 9 cm. Capsule pinkish white. On section tumor was, for the most part, a solid mass of glistening white fibrous tissue. Numerous cyst cavities, ranging in size from 1 to 5 cm. in diameter, contained straw-colored fluid. The walls of these cavities were smooth. Smaller tumor was solid

and ivory-colored and was incorporated with the right ovary. Gross Diagnosis: Bilateral edematous fibromas of the ovaries. Microscopic Diagnosis: Moderately cellular ovarian fibroma.

The patient's convalescence was uncomplicated. She was followed in the clinic for three years, during which time she remained in excellent health and was then lost trace of. There was no evidence during the aforementioned period of any recurrence of fluid in the chest or of tumor masses elsewhere.

DR. WILLIAM W. HERRICK.—I believe that cases of the kind described are more numerous than is ordinarily supposed. Last spring, at the Association of American Physicians, Dr. Watson and I reported another. In the discussion several members of the Association cited cases of a similar sort.

One of the most significant clinical features of this syndrome is that the patients are practically always without fever. Hydrothorax of almost any other cause is at one time or another accompanied by fever. A recurring, afebrile hydrothorax, with or without demonstrable ascites, in a woman over 30 years of age, should arouse suspicion of an ovarian fibroma.

Our patient was a woman of 74 years who came to my office because her children thought she did not look well. She was thin, slight of figure and looked her age, but had very sound essential organs. At the first examination there was slight dullness at the base of the right lung which I interpreted as an old organized pleurisy. This view fitted well with some calcified nodes that the fluoroscopic examination revealed at the hilus. In a few weeks she returned with a fully developed right hydrothorax. This was tapped altogether about nine times. The fluid disclosed no evidence of infection on guinea pig inoculation or ordinary examination. I did not make a pelvic examination until we had performed the thoracentesis about three or four times. When I did, it was quite apparent that there was a tumor of the right ovary of appreciable size. It then occurred to me that I was dealing with Meigs' syndrome and I invoked the aid of Dr. Watson who removed the tumors which he will describe.

Our patient has enjoyed good health ever since her operation, without a trace of recurrence of fluid. One of the most remarkable features of such cases is the rapidity with which the fluid in the chest vanishes after removal of the tumors and the fact that it does not recur.

The experimental work of Dr. Meigs is very important. One might think the negative pressure in the thorax a factor in promoting the transfer of material from the peritoneum into the thorax and preventing progress in the reverse direction. There are a great many conditions, such as cirrhosis of the liver with ascites, in which one has a complicating hydrothorax in which a like mechanism may be operative.

Dr. Meigs' experimental study should throw light upon the general relation of hydrothorax to abdominal conditions other than fibroma of the ovary which may be attended by ascites.

I am sure that internists have failed to recognize many cases of ovarian fibroma with hydrothorax and have condemned these women to needless suffering, if not death, with an erroneous diagnosis of malignancy. I think it is high time that the medical man, as well as the gynecologist, became alert to this important and, I believe, not too uncommon condition.

Dr. Watson will describe the pathology found in the case to which I have alluded.

DR. BENJAMIN P. WATSON.—The physical findings in this case were similar to those which Dr. Meigs has described.

Here there is shown the large tumor on the left side and a smaller fibroma on the right. The pedicle was not particularly long and I do not think that it had ever undergone torsion.

This patient had comparatively little ascitic fluid in the abdomen. Fluid accumulated repeatedly in the right pleural cavity, however. She made an absolutely uneventful recovery, although 74 years of age. Operation was done under intravenous sodium pentothal anesthesia.

Over a period of nine years there have been in the Sloane Hospital nine cases of ovarian fibroma. Only two of these showed gross ascites, although some of the others probably had small quantities of fluid in the abdomen. This is the only case of ovarian fibroma in which I found fluid in the chest.

DR. WILLIAM E. STUDDIFORD.—Since Jan. 1, 1932, about 25,000 patients have been cared for on the gynecologic service at Bellevue Hospital. About 20 per cent, or 5,000 of these patients, were found to be suffering from some sort of gynecologic neoplasm. About 12 per cent of these, or 600 of the patients, had tumors arising in the ovary. Among the ovarian tumors there were 14, or 2.5 per cent of fibromas. None of the latter patients exhibited the syndrome which has been described by Dr. Meigs this evening, and in only one instance was the clinical picture very closely similar. It may be of interest to report this case in some detail.

The patient was 36 years old, white, married, para 0, gravida 0, admitted to the Third Medical Division of Bellevue Hospital on June 6, 1942. Her menstrual history was normal and her past medical and surgical histories were irrelevant. The chief complaint was progressive shortness of breath and gnawing pain beneath the right scapula, first noticed a week or ten days before admission.

Examination showed a slightly dyspneic patient who appeared otherwise to be in good health. Physical signs and roentgenologic examination both showed evidence of right pleural effusion. Examination of the abdomen was negative. Pelvic examination showed a round, firm, movable mass, about 10 cm. in diameter, in the area of the left ovary. The other physical findings were normal. The pulse was 110 and the temperature 98.6° F. Examination of the blood and urine proved normal.

During the first week after admission to the hospital the right chest was tapped on five occasions, from 1,100 to 2,000 c.c. of serous fluid being obtained, and each of the specimens were blood tinged. Tubercle bacilli could not be demonstrated in the sediment, either microscopically or by guinea pig inoculation.

Sections of the sediment showed groups of epithelial cells arranged in rosettes or about a central core of stroma. Differential stains failed to show the presence of mucin in these cells. Roentgenologic and bronchoscopic examination of the lungs failed to show any primary neoplasm.

The patient was transferred to the gynecologic service and a laparotomy performed on July 10, resulting in the removal of a fibroma of the left ovary. No intraperitoneal fluid was present and no other abnormal condition was noted in the abdomen.

Following removal of this tumor no improvement took place in the right chest. Pain and dyspnea continued, and although smaller amounts of fluid were obtained, it was believed that this could be explained by the development of adhesions with resultant loculation of the effusion. It must be assumed that the process in the right pleural cavity was entirely independent of the fibroma in the left ovary.

The patient is still under observation and repeated studies have failed to reveal any neoplasm apart from the pleural cavity or any suggestion of tuberculosis. The thoracic surgeons are now considering exploration of the right pleural cavity to determine the exact nature of the disease.

While this case at the onset closely resembled the condition described this evening in its clinical aspects, it can be easily differentiated by the character of the pleural fluid which, on examination, showed not only red blood cells, but peculiar epithelial elements. These findings have never been described in a case of pleural effusion secondary to fibroma of the ovary.

DR. HOWARD C. TAYLOR, JR.—My contribution to this discussion is the report of one additional case of Meigs' syndrome which I treated last May. The patient was quite typical as far as the previous history and course were concerned. She was 72 years of age and gave a history of about three years of abdominal discomfort. Roentgenologic examinations of the gastrointestinal tract had been made by an internist who saw the patient a few minutes after the onset of symptoms. Ten months before coming to me the patient noticed an abdominal tumor and at about the same time fluid was found in the chest. Thereafter she was for sometime considered to be an inoperable case of carcinoma of the ovary. When she finally came to the Memorial Hospital, the lack of progress of what had been regarded as a malignant condition led to the diagnosis of a fibroma of the ovary.

The patient underwent a thoracentesis and about 500 c.c. of fluid were removed. She was studied carefully before operation and the blood count, plasma protein level and other laboratory data were normal. At operation there was disclosed a typical fibroma of the ovary with moderate ascites. The postoperative course was uneventful and examination six months afterward failed to reveal any fluid in the abdomen or thorax.

I would like to ask whether Dr. Meigs has succeeded in dissociating hydrothorax entirely from the ovarian tumor. Is the appearance of fluid in the chest cavity now to be considered in no sense specific for the ovarian tumor but something which is as likely to occur with ascites from any other cause.

DR. JOE VINCENT MEIGS.—I did not mention that this report covers 27 patients and the three added tonight increases the number to 30. Dr. Herrick said that at his meeting in Atlantic City about six or more were mentioned. The total is a considerable number, especially when it is borne in mind that when we started in 1934 there were only three cases. Many are new and many have been reported in the literature.

One of our patients did have fever. She was operated upon by Dr. Harrington. He became so upset about the case that one day he made a large opening in the chest under local anesthesia, and inserted a tube. An infection developed and he said "that is the end of it, now she has laudable pus, she will get well." But, she did not get well until later when the tumor was removed.

I believe Dr. Armstrong thinks that fluid in the abdomen and chest is not at all specific for the ovary. Any abdominal fluid can get into the chest, as for example, in cirrhosis of the liver. If there is a hole or holes, they may be large or even tiny perforations as Dr. Churchill has suggested. It seems to me that the fluid above the diaphragm is due to lymphatic drainage. However, I do not know. The two fluids are identical as has been shown by electrophoretic studies. I do not think that only an ovarian tumor will do it; I think any fluid in the abdomen may do the same thing. Irritation above the liver in a subdiaphragmatic abscess, for example, may cause fluid above the diaphragm. The chief thing in this discussion is that there is such a syndrome. If we can report 30 such cases there must be many more. We saw three cases last year because we are more on the alert and are looking for such cases. The peritoneoscope should help us.

NUTRITION STUDIES DURING PREGNANCY

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I. Problem, Methods of Study and Group Studied

GROWTH begins with conception, not with birth. Growth requires dietary essentials to a greater extent than maintenance. Although in the earliest part of pregnancy the ovum carries some nutrient material within itself, it must necessarily be dependent upon the mother for the major portion of the material from which it is to grow and develop.

The interrelationship of mother and fetus and the extent of dependence of the fetus upon the maternal diet are problems which must be solved before the role of nutrition in pregnancy can be thoroughly understood. These must be studied through observation of the prenatal diet and general health, both of which may be heavily conditioned by the mother's preconceptional state. Stated specifically, a complete study of the effect of nutrition upon fetal growth and development should attempt to determine: (1) the effect of the mother's preconceptional health and nutrition upon the prenatal course and upon the development of the fetus; (2) the nutritional requirements in respect to pregnancy and the relationship of the mother's preconceptional nutritional state to the requirements of pregnancy; (3) the relative importance of the essential nutrients to the course of pregnancy, labor, delivery, the puerperium and to the development of the fetus and the health of the infant.

While numerous papers on prenatal nutrition in relation to fetal development and the health of the infant have been published, only a few illustrations of fetal damage resulting from prenatal nutritional deficiency will be mentioned. An outstanding illustration is the work of the University of Wisconsin Agricultural Experiment Station[1] on the effects of different rations upon growth and reproduction. These workers found that the corn-fed heifers gave birth to full-term vigorous young, normal in size and able to stand and suck within an hour after birth. They all lived and developed normally, whereas the young of the wheat-fed mothers were born prematurely, were small, and either were stillborn or died within a few hours. The young of the mothers who were fed the oat plant ration or a mixture of the three grains were weak or stillborn. The mothers were continued on the experimental

rations and the following year repeated in all the essential details their previous reproduction records. Evidence of damage to the human fetus from inadequate nutrition in the prenatal period is also to be found.[2-4]

The metabolic studies of Macy and her co-workers[5] and of Coons[6] have added much factual data on the nutritional requirements of women in this period. The recent work of Ebbs, Tisdall and Scott[7] evaluates the diet of the mother in relation to her condition, as well as to the condition of the infant at birth and during the early months of life. An interim report of the Committee of the People's League of Health in England[8] gives interesting statistical data on the effects of improvements in prenatal diet by the use of nutritional concentrates.

Material

The material presented in this paper and those to follow originates in data collected on a selected group of mothers and their children over a period of twelve years and is a part of the research program on the growth and development of the well child undertaken by the Department of Child Hygiene of the Harvard School of Public Health. The work was begun in 1930 and the program enlarged to include the establishment of a Center for Research in Child Health and Development.* Three hundred and twenty-four children have been enrolled at the Center, and approximately two hundred of these children are still actively enrolled. A description of the work at the Center is given in another publication.[9]

The women for this study were chosen from the prenatal clinics of the Boston Lying-in Hospital. The observations during pregnancy, labor, delivery, and the puerperium were made in the early years of the study by the obstetricians of the hospital and later by those on the staff of the Center. These women were seen at least monthly through the seventh month of pregnancy and every two weeks during the eighth month and weekly thereafter, unless seen more frequently because of complications.

At the first visit to the prenatal clinic, a thorough physical examination was made and complete medical and obstetric histories obtained. At all subsequent visits, blood pressure and weight were recorded and the urine examined for albumin and sugar. Careful notations were made of any complications of pregnancy and of any intercurrent illnesses. These data have been supplemented throughout the entire series by periodic nutrition histories, certain social, economic, and other information in regard to the patient and her family.[9] A number of the group in the latter part of the series were included in special studies.[10, 11] Hemoglobin and hematocrit values have been obtained and will form the basis for a special report.

The obstetrician evaluated the condition of the infant at birth, and always within forty-eight hours a physical examination was made also by a pediatrician from the staff of the Center. These observations were augmented by notes from the hospital records. Infants whose neonatal course was not entirely satisfactory were seen frequently by

*The work of the Center was made possible in part under a grant from the General Education Board of the Rockefeller Foundation. The nutrition studies have been supported in part by a grant from the Forsyth Dental Infirmary for Children, Boston.

a pediatrician from the Center, who also examined each infant before discharge from the hospital, usually on the fourteenth day of life. It is upon these data that the pediatric ratings used in this paper and subsequent papers of the series, describing the condition of the infant at birth and within the first two weeks of life, are based.

The nutrition data used in this study were obtained during the first two years by a woman pediatrician and during the last ten years by a trained nutritionist. Dietary histories were obtained at the mother's first visit to the prenatal clinic and at as many subsequent visits as the individual case necessitated, at least once each trimester. These histories include a complete record of the food intake for the twenty-four-hour period preceding the clinic visit, data about the woman's food habits previous to and during pregnancy, food likes and dislikes, amounts of foods purchased, number of persons in the family, amount of money spent for food each week and other related data. In addition, each woman kept at regular intervals a record of food consumed over a consecutive three-day period, which was compared with the dietary history taken by the nutritionist for that period. The amounts usually eaten daily of such important foods as milk, meat, eggs, whole grain products, vegetables and fruit have been carefully investigated, as well as the amounts of highly refined carbohydrate and fat-rich foods. This was carefully studied to learn to what extent these latter types of foods were replacing foods rich in essential proteins, minerals, and vitamins. Such a method of cross-checking important data contributed greatly to the accuracy of the final dietary estimates. Sample forms used in taking these nutrition histories and further details as to the method employed are given in a monograph published by this Center.[9]

The method used in analyzing these nutrition data is described in detail in another publication.[12] In evaluating the diet for the last two trimesters of pregnancy, a rating for each nutritional essential was assigned, based upon comparison with an arbitrary set of values accepted as "optimal." These arbitrary values are given in Table I. In evaluating the diet for the first trimester of pregnancy and for the period previous to pregnancy, the normal nutritional requirements for the average woman, given also in Table I, were chosen as "optimal." It is observed that they approximate the values recommended by the Food and Nutrition Board of the National Research Council.

TABLE I. OPTIMAL DAILY NUTRITIONAL REQUIREMENTS IN PREGNANCY AND THE OPTIMAL NORMAL REQUIREMENTS OF THE AVERAGE WOMAN*

NUTRITIONAL ESSENTIALS	NORMAL	PREGNANCY† (4TH THROUGH 9TH MONTH)
Calories‡	2,200-2,400	2,600-2,800
Protein, Gm.	60	85-100
Calcium, Gm.	0.8	1.5
Phosphorus, Gm.	1.32	2.0
Iron, Mg.	15	20
Vitamin A,§ I.U.	5,000	8,000
Thiamin, Mg.	1.5	2.0
Riboflavin, Mg.	2.0	2.5
Niacin, Mg.	15	18
Ascorbic acid, Mg.	70	100
Vitamin D, I.U.		400-800

*Generally accepted optimal nutritional requirements, according to available data.

†Assuming the changes in the first trimester to be so small as to be negligible.

‡Energy requirements vary with activity, size of the individual, etc.

§The requirement for vitamin A may be less when provided as vitamin A and may be more if provided chiefly in the form of carotene.

An essential nutrient present in the prenatal diet in this "optimal" amount was assigned a rating of "excellent." For example, if the average protein intake from the fourth month of pregnancy amounted to 85 Gm. or more daily, the diet was called "excellent" in protein. When the amount was somewhat less but yet 80 per cent or more of the "optimal" standard, the nutritional essential under consideration has been called "good." It has been called "fair" when 60 to less than 80 per cent of the standard was present. Less than 60 per cent of the "optimal" standard has been called "poor," and if the average intake was under 50 per cent, it has been termed "very poor."

The "mean" general dietary ratings were obtained by assigning a numerical value to each rating, as "very poor" = 0, "poor" = 1, "fair" = 2, "good" = 3, and "excellent" = 4. This has allowed the assignment of a "mean" value to the average dietary intake of each woman during pregnancy and has done much to remove any personal impressions of those analyzing the data in regard to the general adequacy of the diet. It also means that the dietary evaluations are more accurate when used in comparative studies, as their relative relationships to each other are more exact. This made it possible to handle the nutritional data easily and accurately from a statistical standpoint. It should be remembered that owing to the method of deriving the "optimal" nutritional standards (Table I), which involved adding to the accepted minimum requirements a liberal allowance for safety and individual differences in needs, it is possible that a diet rated "fair" may have been at least "good" under certain circumstances.

Observations upon 216 women and their infants will be presented in this paper. In this first series of cases, only the oldest sibling of each family in the study is included. Data on approximately the last 150 cases are derived from a more reliable sampling and represent in each field material more discriminately collected than that on the earlier cases. Group I consists of all cases up to and including Case 150 who were oldest siblings, and Group II, all oldest siblings beyond Case 150. The second group is by necessity somewhat smaller, as the study children beyond Case 150 naturally include many more siblings. Group II also included several women drawn from a special group weighted with cases which had toxemia in previous pregnancies and three women with definite toxemia who had premature infants.* These weightings must be recalled in interpreting the data presented. One hundred and twenty-three cases fall in Group I, and 93 in Group II.

The parents of these infants are largely of Northern European stock, 85.3 per cent in Group I and 92.4 per cent in Group II. From an economic standpoint, the parents were selected to represent the average "middle class" American family with incomes ranging from $25 to $40 per week in the majority of the families.

In Group I, 53 per cent of the women were 25 years of age or less, 28 per cent were between 25 and 30 years, and 19 per cent were over 30 years of age at the time of delivery. In Group II, 40 per cent were 25 years or less, 39 per cent were between 25 and 30 years, and 21 per cent were over 30 years of age.

The number of months of prenatal care received by the mothers is presented in Table II, and in Table III the complications of their pregnancies are given.

*One specialist on the staff of the Center was particularly interested in premature infants.

TABLE II. MONTHS OF PRENATAL CARE

NUMBER OF MONTHS	GROUP I		GROUP II		TOTAL GROUP	
	NO. CASES	%	NO. CASES	%	NO. CASES	%
3 Mo. or less	35	28.5	9	9.7	44	20.4
3½-4 Mo.	31	25.2	15	16.1	46	21.3
Over 4 Mo.—less than 6 Mo.	27	21.9	19	20.4	46	21.3
6 Mo. or more	30	24.4	50	53.8	80	37.0
Totals	123	100	93	100	216	100

From Table III, it is seen that in each group 40 women had complications during the prenatal period: 32 women had one complication, 6 had two, and 2 had three. Only those women in Group II whose hemoglobin levels were found to be below 60 per cent at one or more examinations are included in this table. Hemoglobins below 75 per cent, however, are considered a definite indication of anemia needing treatment. The women in Group II had hemoglobins done regularly as a part of their routine examinations, but this was not the case in Group I, where no woman was described as anemic, unless the anemia was of such a degree as to have been recognized clinically and then confirmed by the laboratory. The difference in the number of cases of anemia noted in the two groups suggests the desirability for routine hemoglobin determinations during the prenatal period.

TABLE III. COMPLICATIONS OF PREGNANCY

	GROUP I		GROUP II		TOTAL GROUP	
	NO. CASES	%*	NO. CASES	%*	NO. CASES	%*
Pre-eclampsia	17	13.8	11	11.8	28	13.0
Nausea and vomiting, severe	6	4.9	10	10.8	16	7.4
Sepsis:						
(1) Salpingitis	1	0.8			1	0.5
(2) Otitis media	1	0.8			1	0.5
Urinary tract infections	3	2.4	2	2.2	5	2.3
Prenatal staining	9	7.3	7	7.5	16	7.4
Heart disease	3	2.4			3	1.4
Anemia	3	2.4	8	8.6	11	5.1
Miscellaneous†	8	6.5	12	12.9	20	9.3
Total number of complications	51		50		101	
Total number of women with complications	40	32.5	40	43	80	37
Total number of women with uncomplicated pregnancy	83	67.5	53	57	136	63

*The figure in this column gives the percentage incidence of each type of complication in relation to the total number of women in each group.

†The miscellaneous group includes blepharitis, pigmented degeneration retina of eye, duodenal ulcer, syphilis, chronic nephritis, leucorrhea, severe epidermophytosis of hands, severe eczema of face, respiratory infections, hydramnios, edema, desquamation of finger tips, fibroids.

Table IV shows the parity of the women under study. The majority of the women in both groups were primiparas.

In every case labor was spontaneous, with the exception of 7 cases of induced labor and 3 cesarean sections without test of labor. The duration of labor is given in Table V, the type of delivery in Table VI, and the complications of labor and delivery in Table VII.

TABLE IV. PARITY

NUMBER OF PREGNANCY	GROUP I		GROUP II		TOTAL GROUP	
	NO. CASES	%	NO. CASES	%	NO. CASES	%
1	80	65.1	66	71.0	146	67.5
2	31	25.2	21	22.6	52	24.1
3	10	8.1	5	5.4	15	6.9
4 to 7	2	1.6	1	1.0	3	1.5
Totals	123	100	93	100	216	100

TABLE V. AVERAGE HOURS OF LABOR*

PARITY	GROUP I		GROUP II		TOTAL GROUP	
	NO. CASES	AVERAGE NO. HR.	NO. CASES	AVERAGE NO. HR.	NO. CASES	AVERAGE NO. HR.
Primiparas	76	16.6	68†	14.9	144	15.8
Multiparas	43	16.0	18	10.4	61	10.1

*All cesarean sections (11) excluded.

†63 primiparas and 5 essential primiparas.

TABLE VI. TYPE OF DELIVERY

	GROUP I		GROUP II		TOTAL GROUP	
	NO. CASES	%	NO. CASES	%	NO. CASES	%
Normal	71*	57.7	41	44.1	112	51.8
Low forceps†	38*	31.0	37	39.8	75	34.7
Midforceps	2*	1.6	3*	3.2	5	2.3
Scanzoni	2‡	1.6	4‡	4.3	6	2.8
Breech extraction	5	4.1	1	1.1	6	2.8
Version extraction	1	0.8	0		1	0.5
Cesarean section	4	3.2	7§	7.5	11	5.1
Totals	123	100	93	100	216	100

*In Group I manual rotation of the head was necessary in one normal, one low forceps and one midforceps case. In Group II one midforceps delivery involved a manual rotation of the head.

†This number of low forceps deliveries should be considered in the light of the policy of the Boston Lying-in Hospital, which provides for delivery by low forceps if the cervix is fully dilated and the head is on the perineum for one hour without progress.

‡In Group I one of the Scanzoni deliveries was also low forceps; the other was midforceps. In Group II all were low forceps.

§One cesarean section was followed by a hysterectomy.

There were no abortions* in this series, but it should be mentioned that almost all of the women in Group I were registered during or following the third month of pregnancy. Data on the termination of the pregnancies studied are given in Table VIII.

Complications during the post-partum period are presented in Table IX.

The distribution of the birth weights of the 216 infants and the distribution of the crown-heel lengths of the infants will be discussed in a subsequent paper.

*The term abortion is used according to the definition of the American Public Health Association: "The term *abortion* should be reserved for the expulsion or extraction of the product of conception previous to its presumed viability, usually understood to apply to a fetus of less than twenty-eight weeks from the assumed date of conception (6½ calendar, or 7 lunar months, at which time, in the races prevailing in the United States, the fetus will weigh 1,500 Gm. or 3¼ pounds and have a length of 35 cm. or 14 inches)."

TABLE VII. COMPLICATIONS OF LABOR AND DELIVERY

	GROUP I		GROUP II		TOTAL GROUP	
	NO. CASES	%*	NO. CASES	%*	NO. CASES	%*
Fetal distress	13	10.6	6	6.5	19	8.8
Excessive blood loss	2	1.6	1	1.1	3	1.4
Placenta previa	2	1.6	2	2.2	4	1.9
Dystocia:						
(1) Primary uterine inertia	4	3.3	3	3.2	7	3.2
(2) Secondary uterine inertia	32	26.0	32	34.4	64	29.6
(3) Disproportion	5	4.1	7	7.5	12	5.5
(4) Malposition	8	6.5	10	10.7	18	8.3
Induction of labor	3	2.4	4	4.3	7	3.2
Retained placenta	1	0.8	1	1.1	2	0.9
Miscellaneous†	6	4.9	11	11.8	17	7.9
Total number of complications	76		77		153	
Total number of women with complications	57	46.3	58	62.4	115	53.2
Total number of women with normal labor and delivery	66	53.7	35	37.6	101	46.8

*The figures in this column give the percentage incidence of each type of complication in relation to the total number of women in each group.

†The miscellaneous group includes prolapsed cord, vaginal laceration, contraction ring, manual extraction, cesarean before term because of preeclampsia, coryza, spontaneous premature rupture of the membranes, separation of old cesarean section scar, and exploration of the uterus.

TABLE VIII. TERMINATION OF PREGNANCY UNDER STUDY

INFANT	GROUP I		GROUP II		TOTAL GROUP	
	NO. CASES	%	NO. CASES	%	NO. CASES	%
Full term	117	95.1	83	89.3	200	92.6
Premature	2	1.6	7*	7.5	9	4.2
Stillborn	4	3.3	1	1.1	5	2.3
Died within 2 hours			2	2.1	2	0.9
Totals	123	100	93	100	216	100

*This group contains 3 infants who were enrolled at the request of one of the examining pediatricians because of their prematurity. The prenatal nutrition data on any case of this type were taken by our nutritionist in the post-partum period in the hospital.

II. Relation of Prenatal Nutrition to Condition of Infant at Birth and During First Two Weeks of Life

In considering the effects which prenatal nutrition may have on infant morbidity and mortality, an investigation was made of the relationship between the diet of the mother during pregnancy and the condition of her infant at birth and within the first two weeks of life. Since limitations of space make it impossible to present in this paper the complete data on all of the 216 infants, only the extremes of the groups (that is, the best and the poorest) are presented.* The pediatric ratings of the infants were studied in relation to the mean general dietary rating assigned to the mother's diet during pregnancy.

*It should be remembered in studying the relationships obtained that the ratings used in each field (pediatric, obstetric, nutritional, anthropometric, etc.) have been made independently on all mothers and their infants under study by the specialist in charge of the particular field, and the results in each field assembled to determine possible associations of statistical significance.

TABLE IX. COMPLICATIONS DURING POST-PARTUM PERIOD

	GROUP I		GROUP II		TOTAL GROUP	
	NO. CASES	%*	NO. CASES	%*	NO. CASES	%*
Elevated temperature	16	13.0	12	12.9	28	13.0
Puerperal sepsis	6†	4.9	5	5.4	11	5.1
Phlebitis			2	2.2	2	0.9
Retention of lochia, subinvolution, and retained secundines	20	16.3	9	8.7	29	13.4
Hemorrhage, post partum	1	0.8	4	4.3	5	2.3
Urinary tract infections	8	6.5	9	9.7	17	7.9
Retention of urine	8	6.5	17	18.3	25	11.6
Post-partum pre-eclampsia	6	4.9	6	6.5	12	5.6
Mastitis	2	1.6	3	3.2	5	2.3
Cervical erosion	2	1.6			2	0.9
Anemia	5	4.1	3	3.2	8	3.7
Heart disease	3	2.4			3	1.4
Miscellaneous‡	15	12.3	10	10.7	25	11.6
Total number of complications	92		80		172	
Total number of women with complications	53	43.1	43	46.2	96	44.4
Total number of women with uncomplicated post-partum period	70	56.9	50	53.8	120	55.6

*The figures in this column give the percentage incidence of each type of complication in relation to the total number of women in each group.

†One patient died eleventh day post partum.

‡The miscellaneous group includes shock, bronchial pneumonia, otitis media, other respiratory infections, perineal fistula, pityriasis rosea, hematoma vagina, ileus, drug reaction, ischemic paralysis, fibroids, lymphadenitis and rectovaginal fistula.

All infants in both groups who were considered to be "superior" were selected. The term "superior" means that the infant at birth and during the first two weeks of life was rated by the pediatrician as of "excellent" or "good" condition, with no physical count of any kind recorded against it. As representative of the other extreme of the group *all* infants were selected who were in the "poorest" condition, that is, were stillborn, died within a few hours or days of life, had a marked congenital malformation at birth, were premature (under 5 pounds at birth), or were "functionally immature." The term "functionally immature" means that the physical development or reactions of the infant were considered below normal in some way and does not apply to weight and length alone. All of the 216 infants not included in the extremes were rated in physical condition somewhere between these two extreme groups.

When the condition of the infants is studied in relation to the mother's mean general dietary rating for the prenatal period, it is found that 56 per cent of the mothers of these infants had had "good" or "excellent" diets, 35 per cent, "fair" diets, while only 9 per cent had had "poor" diets during pregnancy. In contrast, when the condition of the "poorest" infants, i.e., those who were stillborn, etc., is studied in relation to the mother's diet during pregnancy, it is found that 79 per cent of the mothers had diets which were rated as "poor" or "very poor," 18 per cent had "fair" and only 3 per cent had "good" or "excellent" diets during pregnancy. This relationship is shown graphically in Fig. 1.

The average birth weight of the infants considered to be in "superior" physical condition was 8 pounds 2 ounces (range 6 pounds 10 ounces to

11 pounds 7 ounces), and their average birth length* was 20 inches (range 18.5 inches to 21 inches). In contrast, the average birth weight of those infants in the "poorest" physical condition was 5 pounds 15 ounces (range 3 pounds 4 ounces to 8 pounds 15 ounces), and the average birth length was 18.6 inches (range 16 inches to 20.5 inches).

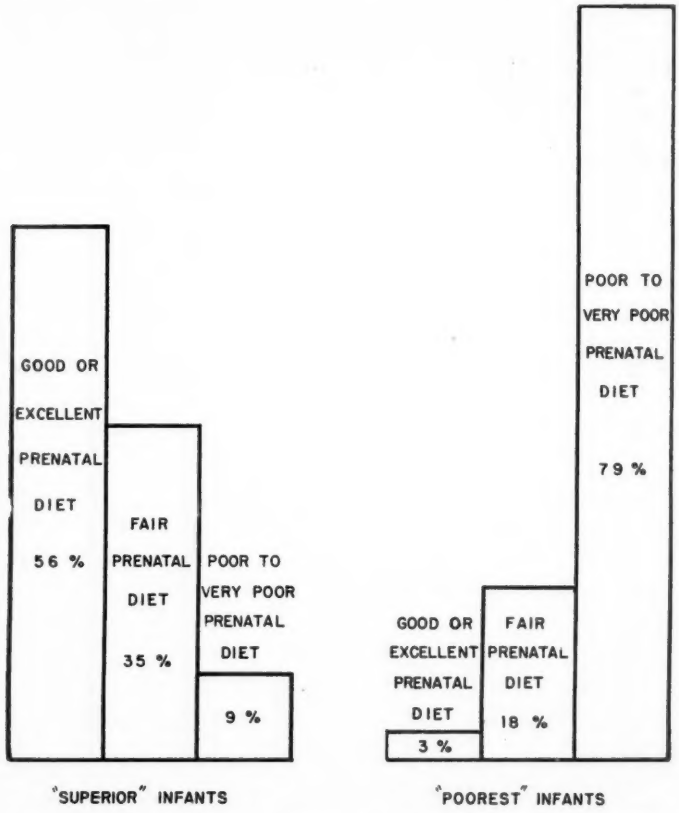

Fig. 1.—Relationship of the condition of the infant at birth and during the first two weeks of life to the mother's diet during pregnancy. (Cases were selected on the basis of pediatric ratings of infants.) "Superior" infants (23): All infants rated at birth and during the first two weeks of life as of "excellent" or "good" condition with no detrimental physical count of any kind. "Poorest" infants (33): All infants who were stillborn or died within a few hours or days (7) (three of these had congenital malformations: multiple anomalies [2], congenital urethral stenosis (1), one died of bronchitis and bronchopneumonia on the 3rd day); infants with marked congenital malformations who lived (9) (malformation of the heart [3] [1 died at 5 months], cleft palate [2], congenital cataracts, premature also [1], congenital mobile funnel chest [1] erythroblastosis mild [1], hydrocephalus arrested, premature also [1]); other premature infants (7); all infants who were "functionally immature" (10).

In order to see if results of equal statistical significance would be obtained, the cases were then selected on the basis of the mother's dietary rating during pregnancy, rather than on the basis of pediatric ratings. *All* of the 216 cases in which the mean general dietary ratings for the prenatal period were "excellent" or "good" were chosen, and the condition of these infants was studied. When the infants selected on the basis of the mother's dietary rating during pregnancy are studied, it is seen that 42 per cent of the infants whose mothers' diets were rated

*Only measurements made by members of our staff are included.

"good" or "excellent" were "superior" infants, 45 per cent had only one physical count each, though of such minor importance in the majority of cases that the pediatric rating was "good," in other words in almost as good physical condition as those termed "superior," 10 per cent had two minor physical counts each, and one infant (3 per cent) had a congenital defect. In contrast, *all* of the 216 cases in which the dietary ratings for pregnancy were "poor to very poor" were selected and the condition of these infants studied. It was found that 67 per cent of the infants born to mothers whose general dietary ratings were "poor to very poor" were stillborn, died within three days of birth, had

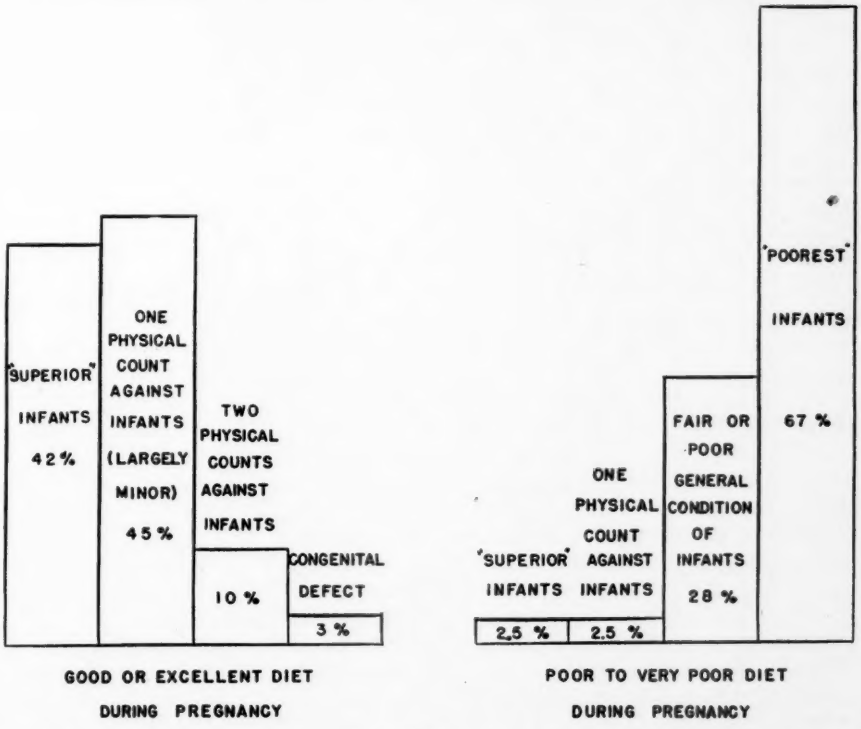

Fig. 2.—Relationship of the mother's diet during pregnancy to the condition of the infant at birth and during the first two weeks of life. (Cases selected on the basis of mother's dietary ratings during pregnancy.) Infants whose mother's diet during pregnancy were "excellent" or "good" (31): "Superior" infants 13 (these are 13 of the 23 "superior" infants shown in Fig. 1); infants with one physical count (largely minor) against each (14), these were small umbilical hernia (4), cephalhematoma (2), subconjunctival hemorrhage (1), conjunctivitis (3), throat infection (1), small hemangioma (1), scalp infection (1), webbed toes (1). Infants with two physical counts (also minor) against each (3): These were receding lower jaw and apathetic (1), conjunctivitis and asphyxia or cyanosis (2). Infant (1) with congenital heart (this infant appears in the "poorest" group in Fig. 1). Infants whose mothers' diet during pregnancy was "poor to very poor" (36): "poorest" infants (24) (these are 24 of the 33 "poorest" infants in Fig. 1), stillborn or died within few hours or days (7) (2 of these had congenital malformations, multiple anomalies [1] and congenital urethral stenosis [1]), one was also premature, one died of bronchitis and bronchopneumonia third day). Infants with marked congenital defects who lived (6) (congenital heart [2], 1 died at 5 months, congenital cataracts, premature also [1]; a mentally retarded child, erythroblastosis, mild [1], hydrocephalus, arrested, also premature [1]; cleft palate [1]; a feeble-minded child). Other premature infants (5); infants who were "functionally immature" (6); infants in fair or poor general condition (10) (malnutrition [1], hyperirritability in varying degrees [3], calcaneo valgus deformity and hemangioma [1], strabismus and condition otherwise fair [1], functional maturity fair [3], skin infection [?], thrush and otherwise fair [1]); infant condition good except for small umbilical hernia (1); "superior" infant (1) (this infant is one of the superior infants in Fig. 1).

congenital defects, were premature or "functionally immature," 28 per cent were considered to be in "fair" or "poor" general condition, and only 5 per cent were in "good" or "excellent" condition. These results are shown graphically in Fig. 2. It should be emphasized that practically all the infants born to mothers receiving "good" or "excellent" diets during pregnancy who were not called "superior" had only slight defects, such as mild transient conjunctivitis, small umbilical hernia, small hemangioma, etc. Actually, all but one infant born to these mothers with "good" or "excellent" diets during pregnancy were in "good" condition at birth, while only 2 infants born to mothers with "poor to very poor" diets during pregnancy were in "good" condition at birth.

Likewise, when considering birth weights and lengths of infants selected on the basis of the mother's diet, an average weight of 8 pounds 8 ounces (range 6 pounds 12 ounces to 11 pounds 7 ounces) and an average length of 20.4 inches (range 18.5 inches to 21.5 inches) were found for those infants whose mothers had superior diets during pregnancy. The average birth weight of the infants whose mothers' diets were rated "poor to very poor" was 5 pounds 13 ounces (range 3 pounds 4 ounces to 8 pounds 15 ounces), and the average birth length was 18.6 inches (range 16 inches to 20.75 inches).

The fact that the relationships are similar whether the cases are selected from the standpoint of the condition of the infant or selected on the basis of the rating assigned to the mother's diet during pregnancy makes this relationship which exists between the mother's diet and the condition of her infant of even greater statistical significance. There can be no doubt from these findings that, if the mother's diet during pregnancy is poor to very poor, she will in all probability have a poor infant from the standpoint of physical condition. If the mother has a good or excellent diet, she will probably have an infant in good or excellent condition, but occasionally a mother whose diet in the prenatal period is good will have a poor infant. It is important to note that of the total 216 cases, 132 cases are between the two extremes in both pediatric and dietary ratings, so that the same relationship exists between the condition of these remaining infants in the group and their mothers' nutrition in the prenatal period. This further emphasizes the important relationship existing between prenatal diet and the resulting condition of the infant.

III. The Relation of Prenatal Nutrition to Pregnancy, Labor, Delivery, and the Post-Partum Period

The Course of Pregnancy.—The course of pregnancy was considered normal in 68 per cent of the cases in which the mean general dietary rating for the period of pregnancy was "excellent" or "good"; complications were found in 32 per cent of these cases. Of the cases in which the dietary rating for the prenatal period was "poor to very poor," only 42 per cent of the women experienced a normal prenatal course, while 58 per cent had complications. These relationships are shown graphically in Fig. 3. While there is a statistically significant relationship between the mother's dietary rating and the course of her pregnancy, it is also evident that this relationship is not as marked as that existing between the mother's dietary rating for the period of pregnancy and the condition of her infant. This indicates that with an

inadequate prenatal diet the fetus suffers to a greater degree than the mother. In other words, the fetus is parasitic upon the mother only to a certain extent, and that extent is limited apparently by the mother's nutritional state at the time she enters pregnancy and by the quality and quantity of her diet during pregnancy. It is of utmost importance to realize this fact, because in the usual clinical examination during pregnancy it is not possible to evaluate adequately the condition of the fetus, and it is entirely possible that a woman may have an apparently satisfactory clinical course, but if she is consuming an inadequate diet, the fetus will suffer. Contrary to the usual obstetric teaching, the health of the fetus is greatly dependent on the mother's nutrition during pregnancy.

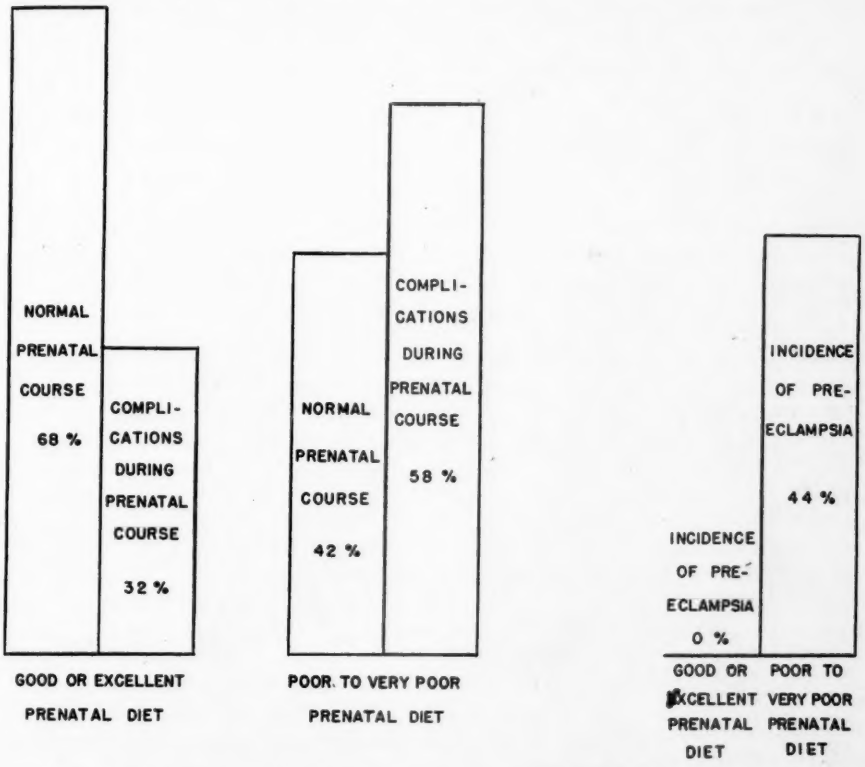

Fig. 3.—Relationship of the prenatal course to the mother's diet during pregnancy. Incidence of pre-eclampsia in relation to the mother's diet during pregnancy. Of the women (31) whose diets during pregnancy were "excellent" or "good," 21 had a normal prenatal course, 10 had complications, such as severe nausea (4), rheumatic heart disease (no failure [1], marked anemia [1]), severe epidermophytosis of hands (1), duodenal ulcer (1), edema (1), staining (1). Of the women (36) whose diets during pregnancy were "poor to very poor" 15 had a normal prenatal course, 21 had complications as follows: pre-eclampsia (16) (nine had other complications as well), pernicious vomiting and severe anemia (1), marked anemia (3), staining (1).

The greater incidence of complications during pregnancy among the women with a "poor to very poor" diet is due largely to a high incidence of pre-eclampsia in this group. While there was no incidence of pre-eclampsia in any pregnancy where the diet was rated either "excellent" or "good," there was an incidence of 44 per cent among the women whose diets during pregnancy were rated "poor to very poor." This is shown graphically in Fig. 3. There was an 8 per cent incidence

of pre-eclampsia in the intermediate group of 132 women. It appears that a significant relationship exists between prenatal nutrition and the incidence of pre-eclampsia in pregnancy. A good or excellent diet during pregnancy would seem to assure its absence, but with a poor to very poor diet during pregnancy, the mother runs an almost 50 per cent chance of having pre-eclampsia.

Labor and Delivery.—The average number of hours of labor of all the primiparas whose diets during pregnancy were rated "good" or "excellent" was 14, and this same figure was obtained for the primiparas whose dietary ratings were "poor to very poor," including the tests of labor made in two cases of cesarean section. If the test hours of labor of these cesarean sections are excluded, the average number of hours of labor of the primiparas of this group was 12. The average number of hours of labor of all multiparas whose diets were rated "excellent" or "good" was 8, while for the multiparas whose dietary ratings during pregnancy were "poor to very poor," the average number of hours of labor was 12. If one considers the types of delivery found in the two diet groups, no cesarean sections had to be performed upon mothers whose diets were "good" or "excellent" during the prenatal period, while 4 cesarean sections were found necessary for women in the "poor to very poor" diet group. There is also a higher percentage of other difficult type deliveries in the "poor to very poor" diet group. This is interesting, since the average birth weight of these infants was markedly lower than that of infants born to mothers whose diets during pregnancy were rated "good" or "excellent." In a consideration of the complications experienced by these women at delivery, only a slightly larger percentage of women, 58 per cent, whose diets during pregnancy were rated "good" or "excellent" experienced a normal delivery than was the case for all women whose diets were rated "poor to very poor"; in the latter group, 50 per cent experienced no complications. If the complications of delivery are classified as *minor* and *major,* it is evident that while the incidence of minor complications was approximately the same in both diet groups, 18 and 14 per cent, respectively, 36 per cent of the "poor to very poor" group had major complications, while in the "good" or "excellent" diet group only 24 per cent had major complications. There was also a greater incidence of fetal distress at delivery among the "poor to very poor" diet group.

It is apparent that any relationship existing between prenatal nutrition and the course of labor and delivery is not clear from this series of cases. The types of labor experienced appear to be more difficult in the "poor to very poor" diet group, despite the fact that the infants born to these mothers were smaller. The incidence of major complications is also higher in the "poor to very poor" diet group. The results from this study do not show a distinct relationship between prenatal nutrition and the character of labor and delivery, as was claimed by Ebbs, Tisdall, and Scott,[7] nor would we concur entirely in these respects with the findings in the Interim Report of the People's League of Health of England.[8] These workers reported that they found no appreciable influence of nutrition on the character and duration of labor. It is entirely possible that a relationship may exist between prenatal nutrition and the duration of labor and the character of delivery; if such a relationship exists, we are inclined to believe that it is much less marked than that found with the course of pregnancy, and that many other factors are involved. Among these factors may be the

nutrition of the mother during her own fetal and postnatal development. Because of dietary habits it is probable that persons with poor diets at one period in life would also have had poor diets at earlier periods and that they may belong to families whose dietary habits were poor.

The Post-Partum Period.—When the post-partum course of all mothers whose diets for the period of pregnancy were rated "excellent" or "good" is compared with the puerperium of all women whose diets during pregnancy were rated "poor to very poor," it is found that an approximately equal number (58 and 56 per cent) of women in each diet group experienced a normal post-partum course. If the complications experienced by these women in the puerperium are separated into *minor* and *major,* it is found that 34 per cent of the women on "excellent" or "good" diets experienced minor complications, and 8 per cent, major complications. With those on the "poor to very poor" prenatal diets, 21 per cent had minor complications, and 23 per cent experienced major complications. The incidence of such major complications as puerperal sepsis is so small in the group studied as to make any conclusions unjustifiable. From the present study, it is evident that while there is a tendency for a relationship to exist between prenatal nutrition and major complications in the post-partum period, there is no distinct relationship such as has been shown with the course of pregnancy.

Conclusions

1. This study has shown a statistically significant relationship between diet of the mother during pregnancy and the condition of her infant at birth.

2. If the diet of the mother during pregnancy is poor to very poor, she will in all probability have a poor infant from the standpoint of physical condition. In the 216 cases studied, every stillborn infant, every infant who died within a few days of birth, with the exception of one, the majority of infants with marked congenital defects, all premature, and all "functionally immature" infants were born to mothers whose diets during pregnancy were very inadequate.

3. If the mother's diet during pregnancy is excellent or good, her infant will probably be in good or excellent physical condition. However, it may happen occasionally (1 out of 216 cases in this series) that a mother whose diet during pregnancy was "excellent" or "good" will give birth to an infant in poor physical condition.

4. A statistically significant relationship was found to exist between prenatal diet and the course of pregnancy. This relationship, however, is not as marked as that existing between the prenatal dietary rating and the condition of the infant. This indicates that when nutrition during pregnancy is inadequate, the fetus suffers to a greater degree than the mother.

5. In this study, no mother whose diet during pregnancy was considered "good" or "excellent" had pre-eclampsia, while with a "poor to very poor" diet during pregnancy, almost 50 per cent had pre-eclampsia.

6. No statistically significant associations were found to exist between prenatal nutrition and the duration and character of labor and delivery.

There was a tendency for the mothers whose diets during pregnancy were "poor to very poor" to have more difficult types of labor and to have more major complications at delivery, despite the fact that these women had, on the average, smaller infants than were born to the women whose diets were "good" or "excellent."

7. No relationships of statistical significance were found to exist between prenatal nutrition and the post-partum course. There seemed to be a tendency toward a relationship between prenatal nutrition and the occurrence of major complications in the puerperium.

The authors are indebted to Miss Jane Worcester of the Department of Vital Statistics for statistical assistance in the handling of the material included in this paper, to Mrs. Vernette S. Vickers Harding of the Center for Research in Child Health and Development, Harvard School of Public Health for valuable assistance in the assembling of the data, and to Dr. F. J. Stare, Division of Nutrition, School of Medicine and School of Public Health, Harvard University, for assistance in the preparation of the paper.

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This disease leads to a stunting of bones preformed in cartilage. Bones developing in membranes are but infrequently involved. This condition is to be differentiated from hereditary deforming chondrodysplasia. The latter disease appears early in childhood and is rarely if ever fatal. In achondroplasia, the disturbance is confined to the epiphyseal cartilages, while in the latter the exostoses arise from the diaphyseal side of the epiphyseal line. The condition is rare among Negroes. The condition is hereditary and is inherited according to the Mendelian order. Hydramnios may be an influential factor in the etiology due to increased intrauterine pressure. These patients are always bright or even above average in mental capacity.

All dwarfs are not achondroplastics. In chondroosteodystrophy seen in children and in young adults, the epiphyses appear late and develop slowly. The softening of the bones is due to calcium deficiency. The skull is large but normal, and the vertebrae are flattened. In the female, the pelvic outlet is decreased, while the obturator foramina are enlarged. The bones of the pelvis seem soft and partly decalcified, and x-ray pelvimetry is important if these patients anticipate pregnancy.

WILLIAM BERMAN.

DETECTION OF OVULATION BY THE BASAL TEMPERATURE CURVE WITH CORRELATING ENDOMETRIAL STUDIES

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OVULATION is an essential link in the chain of events leading to pregnancy. It is now generally recognized that ovulation usually occurs near the midpoint of a normal menstrual cycle, but it has been established also that menstrual cycles and menstruation can occur without ovulation.[1-3] Moreover, such anovulatory cycles may occur in apparently healthy young women who have regular periods and no gynecologic complaints.[4] Since failure of ovulation has been recognized as one of the causes of sterility its detection is an important step in the solution of almost every female sterility problem.

Direct observation of follicle rupture and discharge of ova is not ordinarily possible in human beings so that indirect methods are necessary to detect ovulation. A number of such indirect methods have been offered by different authors, but each method lacks direct confirmation and each is attended by disadvantages in the routine sterility study of private patients.

1. Certain symptoms occurring near the midintermenstruum are suggestive of ovulation. Follicle rupture may produce severe lower abdominal pain or dull lower abdominal pain. Slight discharge, slight bleeding, and dyspareunia are occasional complaints associated with ovulation. These symptoms are frequently more definite if the adnexa have been the seat of previous inflammatory reactions. Pelvic examination at the time of ovulation may disclose a clear, glairy type of mucus coming from the cervix, a tender ovary, and occasionally a little blood in the cervix. These symptoms and signs are not in themselves conclusive evidence of ovulation.

2. The consecutive vaginal smear method which follows the changes in the different types of desquamated cells, was developed by Papanicolaou[5] and has since been used clinically to a considerable extent. A characteristic cell picture is obtained at the time of supposed ovulation. This method is reportedly accurate in determining the date of ovulation within two or three days, but it is cumbersome for routine office practice. The process of fixing and staining the smears is time-consuming and an extensive experience is necessary for accurate interpretation of the smears. Moreover, the character of the smear is changed by douching, intercourse, vaginal infections, and cervical erosions, and artefacts must be carefully eliminated.

3. A definite change in bioelectric potential at the time of ovulation has been reported both in animals[6] and in women.[7] This method is also time-consuming since fifteen to sixty minutes of daily observation are necessary and since the method requires a complicated electrical apparatus. Artefacts again distort the observations and careful precautions must be taken against them.[8]

4. The daily measurement of the hydrogen ion concentration of vaginal secretions for timing ovulation in women was suggested by Zuck and Duncan.[9] The pH of vaginal secretions was found to rise in a characteristic manner at the time an ovulative smear was obtained and a basal body temperature shift was observed. This method requires daily observation and its accuracy even in the absence of abnormal vaginal flow is not well established.

5. The presence in the urine of sodium pregnanediol glucuronidate, an excretion product of progesterone, is evidence of luteal activity and therefore is evidence that ovulation has occurred.[10] Its absence, however, does not prove the absence of ovulation since extraovarian factors may participate in the metabolism of progesterone and its metabolites may not appear in the urine.[11] This method for detecting ovulation has been frequently used in research centers, but at present it is neither practical nor available for ordinary private practice.

6. The most widely used and generally accepted method for the indirect determination of ovulation in women is the premenstrual endometrial biopsy. A secretory type of endometrium reflects the influence of progesterone which is secreted by the corpus luteum and a corpus luteum presupposes follicle rupture. On the other hand, a proliferative type of premenstrual endometrium strongly suggests the absence of ovulation. A number of disadvantages attend the endometrial biopsy for routine clinical use: (1) some pain and bleeding are usually experienced by the patient; (2) if ovulation is delayed a biopsy which is supposedly premenstrual may be taken before the follicle ruptures so that the secretory phase is missed; (3) a beginning pregnancy may be interrupted by an endometrial biopsy before the pregnancy is recognized clinically; (4) the preparation, fixing, and staining of slides require the cooperation of an experienced technician or a pathologist; (5) the date of ovulation is not revealed by endometrial biopsy unless specimens happen to be taken both just before and just after ovulation.

None of these methods completely fills the need for a painless, convenient, yet reliable means of detecting ovulation. It has been suggested that an answer to this problem may be found in the use of basal temperature curves.

Basal temperatures were used by Van de Velde in 1904[12] to study the cyclical ovarian function of women. He described the characteristic two-phase curve which he correlated with cyclical changes in ovarian function. More recently, and in the light of present-day under-

standing of ovarian function, Rubenstein,[13, 14] Palmer and Devillers[15] and Zuck[16] have used basal temperature curves for the study of ovulation and female functional sterility. Palmer[17] has described the use of basal temperature curves for the study of functional sterility and a variety of other functional ovarian disorders.

It has been repeatedly observed that basal temperature curves of regularly menstruating women usually fluctuate in a rhythmical manner. A typical curve begins to fall just before menstruation and reaches a relatively low level just after menstruation. It remains at this level during the first or estrin phase of the cycle. At about the middle of the intermenstruum the curve rises rather suddenly to a higher level, at which it remains during the second or progestin phase. Just before menstruation the curve again begins to fall, unless pregnancy has occurred in which case it remains at its relatively high level. It is probable that this cyclical fluctuation of basal body temperature is either caused by or related to the activity of the two principal ovarian hormones, since an injection of estradiol benzoate will depress the basal temperature, and an injection of progesterone will raise it.[16]

There is evidence to support the contention that the midcycle rise in basal temperature (thermal shift) coincides approximately with ovulation. Rubenstein has found that the thermal shift occurs at the same time that the "ovulative smear" is obtained.[13] Zuck and Duncan have reported a correlation between the thermal shift and the hydrogen ion concentration of the vaginal secretion, and between the thermal shift and the presence of pregnanediol glucuronidate in the urine.[9] Barton has reported a correlation between the thermal shift and the change in bioelectric potential.[18] Zuck has reported that the time of maximum fertility is on the day preceding the midcycle rise in temperature.[17] Furthermore, the basal temperature curves of women who are past the menopause (and of men) do not show rhythmical variation.

Occasionally the basal temperature curve of a menstrual cycle will not show the two-phase characteristic. Such one-phase cycles, without thermal shifts, have been considered anovulatory, but since they are relatively uncommon, they have not previously been systematically checked with other methods of detecting ovulation as have the two-phase cycles.

In the absence of convincing evidence of the significance of changes in basal temperatures, this method has been utilized by only a few workers and its reliability has been questioned by others. In the present study, a further check on the reliability of the basal temperature curve as an indicator of ovulation and ovarian activity has been made by means of the most commonly used method of determining ovulation, namely, the premenstrual endometrial biopsy. Both biphasic and monophasic curves have been checked by premenstrual endometrial findings.

Basal temperatures were recorded through 206 menstrual cycles by 112 private patients of the author. All were between the ages of 16

and 45 years, and all were menstruating with varying regularity. Twenty-two curves from 13 patients were discarded because they were incomplete, or the thermometer was read incorrectly, or the instructions for taking the temperatures were not followed. The remaining 181 cycles from 99 patients were used for this analysis.

The basal temperature curves from 164 complete cycles were definitely biphasic in character, that is, they showed a relatively low level during the estrin phase which follows menstruation and a relatively higher level during the secretory phase which follows ovulation. Typical

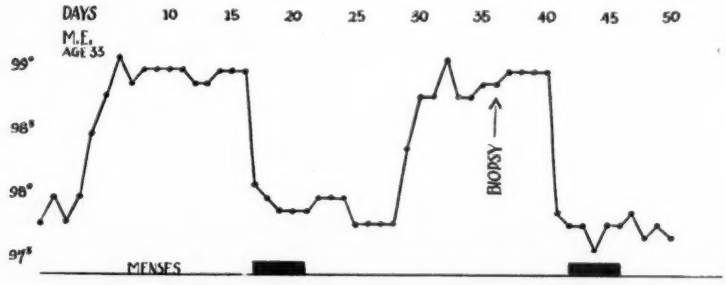

Fig. 1.—Typical biphasic temperature curve.

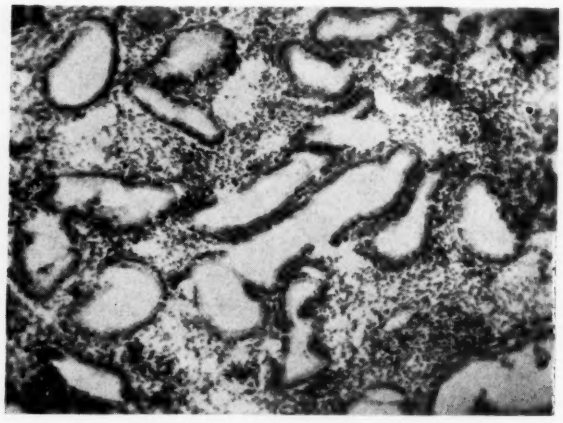

Fig. 2.—Photomicrograph of premenstrual biopsy specimen of patient whose temperature curve is shown in Fig. 1, secretory type of endometrium.

two-phase curves are reproduced in Figs. 1 and 3. Premenstrual endometrial biopsies were taken whenever verification of ovulation was important to the patient and if endometrial biopsy was not contraindicated by a possible beginning pregnancy. By this means premenstrual endometrial studies were made available for correlation with 47 biphasic temperature curves. In every instance the premenstrual endometrium was found to be of the secretory type (Figs. 2 and 4).

Biphasic curves were found in women whose periods occurred every twenty days as well as in women whose periods occurred at intervals

of sixty to ninety days. But the two phases of the cycle did not vary equally in length in such instances. The variation was limited almost entirely to the duration of the first or estrin phase, measured from the onset of menstruation to the thermal shift. The second or progestin phase was of relatively constant duration, from ten to sixteen days. In the 14 curves in which the progestin phase persisted for more than eighteen days, pregnancy was diagnosed and subsequently confirmed in each instance.

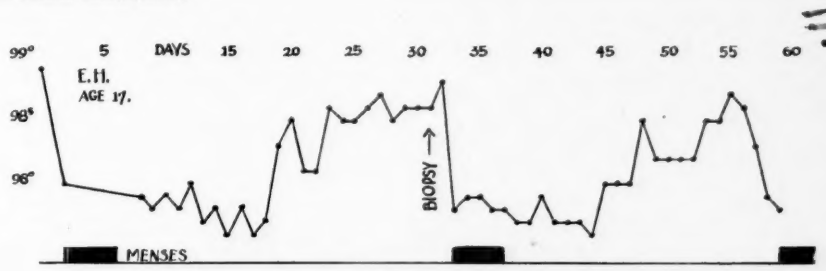

Fig. 3.—Typical biphasic temperature curve.

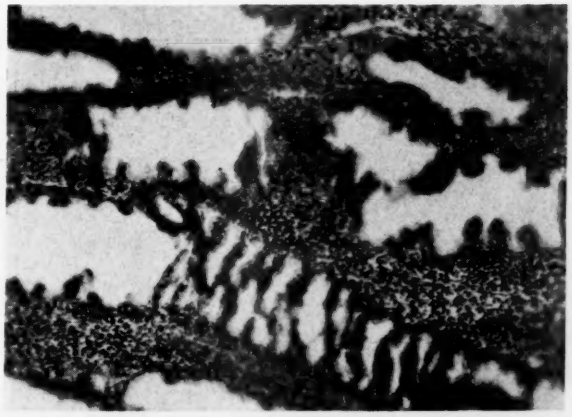

Fig. 4.—Photomicrograph of premenstrual biopsy specimen of patient whose temperature curve is shown in Fig. 3, secretory type of endometrium.

In 17 cycles recorded by 12 patients, the temperature curve was monophasic in character. No thermal shift could be recognized and the premenstrual portion of the curve was about as low as the postmenstrual portion (Figs. 5, 7, 9). In 9 of the 17 monophasic cycles a premenstrual biopsy was taken and in each instance a proliferative type of endometrium was found (Figs. 6, 8, 10). Thus, within the limits of endometrial biopsy as a test, these single-phase cycles were without evidence of luteal activity and were therefore probably anovulatory. Six of these apparently anovulatory cycles were spontaneous and 11 were induced by the administration of stilbestrol during the first three weeks of the cycle. The stilbestrol was given in an attempt to inhibit ovulation in

the experimental treatment of dysmenorrhea. Each menstrual period following a one-phase cycle was characterized by the absence of menstrual cramps, but was otherwise not recognized by the patient as abnormal.

Thus in 56 cycles which were checked by endometrial biopsy, no exceptions were found in the correlation of biphasic cycles and secretory premenstrual endometrium and of monophasic cycles and proliferative premenstrual endometrium.

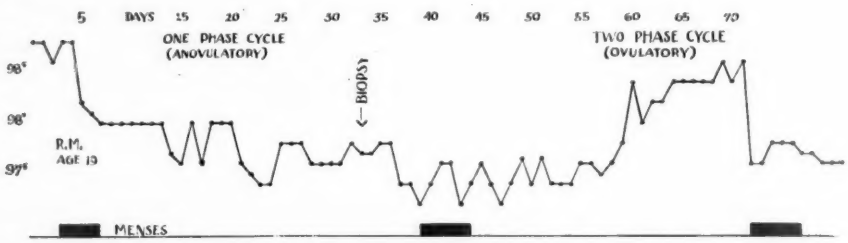

Fig. 5.—Temperature curve showing monophasic cycle followed by biphasic cycle.

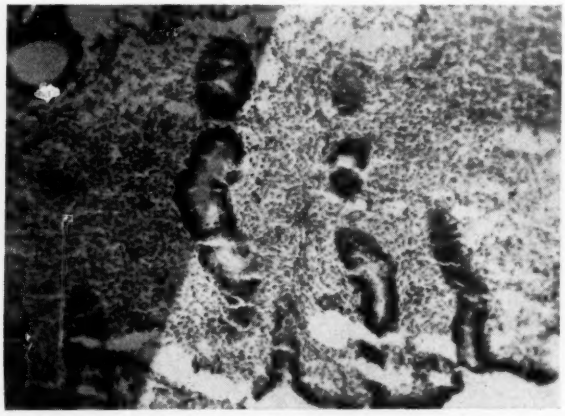

Fig. 6.—Photomicrograph of premenstrual biopsy specimen taken during monophasic cycle of patient whose temperature curve is shown in Fig. 5, proliferative type of endometrium.

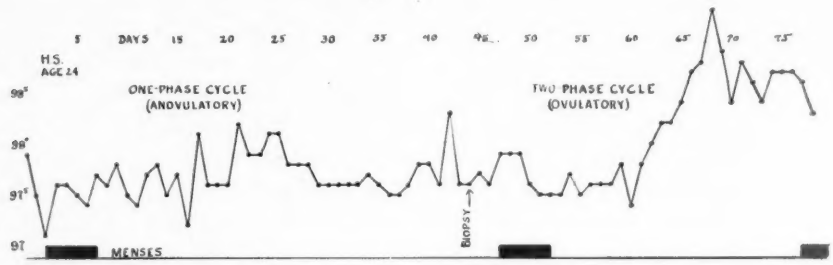

Fig. 7.—Temperature curve showing monophasic cycle followed by biphasic cycle.

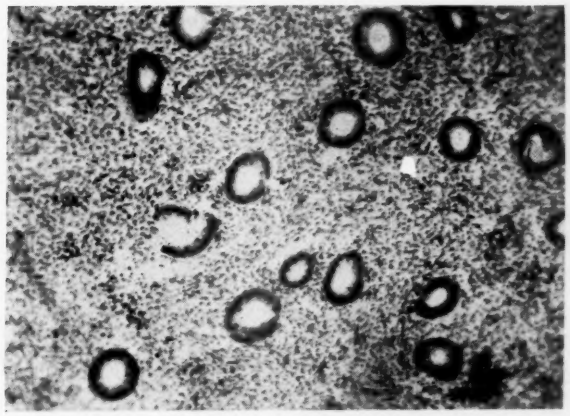

Fig. 8.—Photomicrograph of premenstrual biopsy specimen taken during monophasic cycle of patient whose temperature curve is shown in Fig. 7, proliferative type of endometrium.

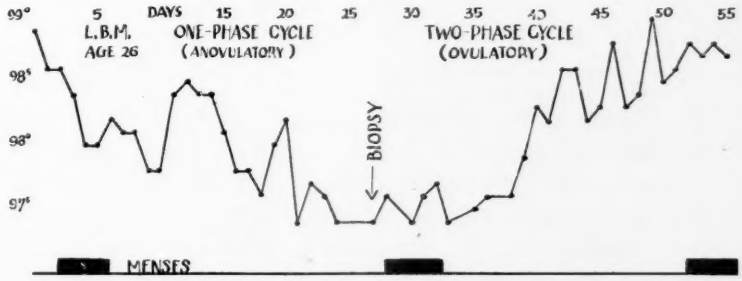

Fig. 9.—Temperature curve showing monophasic cycle followed by biphasic cycle.

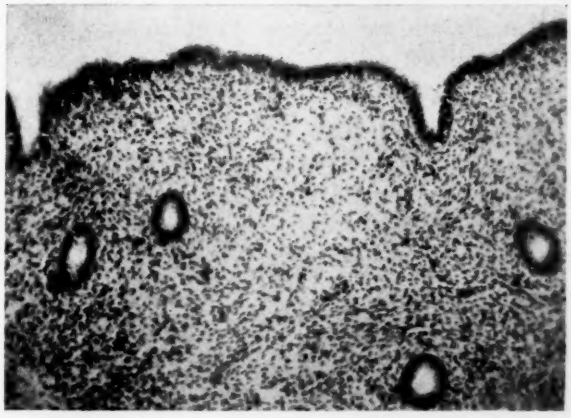

Fig. 10.—Photomicrograph of premenstrual biopsy specimen taken during monophasic cycle of patient whose temperature curve is shown in Fig. 9, proliferative type of endometrium.

In order to determine the reality and significance of basal temperature changes during the menstrual cycle, a statistical analysis of the temperatures recorded in 181 curves was made. The mean temperature for each phase of each cycle (the period of menstrual flow, the period from the end of menstruation to the thermal shift, and the period from the thermal shift to the onset of flow) with its standard deviation was calculated according to the methods of Fisher.[19] Cycles without thermal shifts were divided into two equal parts for comparison. The mean temperatures for each phase or half are compared in Table I.

TABLE I. MEAN AND STANDARD DEVIATION OF DAILY BASAL TEMPERATURES IN 164 BIPHASIC CYCLES AND 17 MONOPHASIC CYCLES

	PERIOD OF MENSTRUAL FLOW	END OF MENSTRUATION TO THERMAL SHIFT	THERMAL SHIFT TO MENSTRUATION
Cycles with Thermal Shift (Biphasic)	98.25 ± 0.28	98.00 ± 0.22	98.60 ± 0.22
		FIRST HALF OF INTERMENSTRUUM	SECOND HALF OF INTERMENSTRUUM
Cycles without Thermal Shift (Monophasic)	97.98 ± 0.26	97.98 ± 0.33	97.91 ± 0.34

The mean temperature of the second or premenstrual phase of the biphasic curves was found to be 0.6 ± 0.04 degree higher than the mean temperature of the first or postmenstrual phase. There was some variation in the mean postmenstrual and premenstrual temperatures of different individuals but there was no exception to the fact that the mean premenstrual temperature of any one person was 0.3° to 1.0° F. higher than her corresponding postmenstrual temperature. The difference of 0.6° between the means of all of the post- and premenstrual temperatures may appear small but considering the small variance and the relatively small standard error of the difference, this difference is enormously significant. On the other hand, the mean temperature difference between the two halves of the monophasic cycles was but 0.07 which, considering the standard error of 0.33, is not statistically significant.

Eight additional basal temperature curves of patients who did not menstruate are of interest. Four were of women whose uteri had been removed surgically, but ovarian function conserved, from one to six years previously. In each case, the basal temperature curve showed regular cyclical fluctuations in all ways similar to the fluctuation of the common two-phase curve of a regularly menstruating woman. The four remaining temperature curves of patients who did not menstruate showed no cyclical fluctuation. Two of these were curves of postmenopausal women; one was of a woman 24 years of age whose vagina was congenitally absent and in whom at laparotomy no uterus or adnexa could be found; and one was of a man, 31 years of age.

A combined temperature and symptom chart was found to be a convenient and time-saving aid in the office study of ovarian function of private patients. Furthermore, patients were found to be interested in their own temperature curves, and it was felt that this daily reminder of their problem stimulated closer cooperation. The instructions require but a few minutes of explanation at the first office visit, and by using this chart, patients of average intelligence are able to keep a record which is sufficiently accurate and complete for clinical use.

Rectal or vaginal temperatures are taken by the patient immediately upon awakening and at about the same time each morning after a restful night's sleep. During this procedure important symptoms are recorded for the previous day. Even if office visits are made but once or twice a month a detailed record of correlating ovarian activity (as reflected in the basal temperatures) and symptoms is available at each visit. Occasionally a patient will sleep late or otherwise vary the technique enough to produce an isolated rise in the basal temperature curve, but such an artefact can usually be recognized at a glance by its deviation from the usual pattern. The relatively constant climate of Southern California did not appear to exert an influence upon the basal temperature, though climate might be a cause for artefacts in other localities.

Summary

Since failure to ovulate is one of the causes of functional sterility in women, there is need of a simple yet reliable method for the detection of ovulation. The basal temperature curve has been previously presented as a simple means for detecting ovulation but its reliability has been open to question. One hundred and eighty-one menstrual cycles were studied by means of basal temperature curves and in 56 cycles the significance of the curve was checked by endometrial biopsy. In 164 cycles the basal temperature curve was biphasic and in each of the 47 of these cycles that were checked by premenstrual endometrial biopsy a secretory pattern of endometrium was obtained, indicating that ovulation had taken place. In 17 cycles, the curves were monophasic in character and in each of 9 which were checked with premenstrual endometrial biopsy, a proliferative type of endometrium was found, indicating that ovulation had not taken place.

A statistical analysis of the recorded temperatures revealed a statistically significant difference between the mean temperatures of the pre- and postmenstrual phases of the biphasic cycles and no significant difference between the mean temperatures of the two equal parts of the monophasic cycles.

These observations are presented as additional evidence, within the limits of endometrial biopsy as a test, and within the limits of a rela-

tively small number of cases, that a biphasic basal temperature curve represents an ovulatory cycle and a monophasic curve represents an anovulatory cycle. It follows that the basal temperature curve offers a possible means of differentiation between ovulatory and anovulatory cycles.

I wish to express my sincere appreciation to H. S. Sumerlin, M.D., for the preparation, examination, and interpretation of the endometrial biopsy specimens, and to Paul B. Donovan, Ph.D., for the statistical analysis of the recorded temperatures.

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Watson, M. C.: Congenital Absence of the Vagina, Canad. M. A. J. **45**: 69, 1941.

The author reports a case of congenital absence of the vagina in an 18-year-old girl successfully treated with the application of pressure by the use of dilators according to the method first described by Robert T. Frank.

Carl P. Huber.

THE RATE OF FILTRATION THROUGH THE CAPILLARY WALLS IN PREGNANCY*

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IT HAS been suggested [1-6] that one cause of edema in pregnancy, both normal and toxemic, may be increased permeability of the capillary wall, but this has never been clearly demonstrated. This study was undertaken to determine whether the concept of increased capillary permeability in pregnancy could be supported by demonstration of changes in the rate of filtration of fluid through the capillary walls into the tissue spaces. While such deviations from the normal might be to some extent the result of factors other than the state of the capillary wall, none of the other well-recognized causes of edema formation has, as yet, explained adequately the generalized edema of pregnancy.[2]

The method of measuring rate of filtration was that employing the pressure plethysmograph.[7, 8] The apparatus and its use have been described elsewhere in detail.[8-10] Briefly, the volume of a segment of forearm with its blood vessels collapsed was measured repeatedly until a relatively constant value was obtained. Filtration then was effected by raising venous pressure in the forearm, and finally the volume of the segment was remeasured. The actual increase in volume of the segment during ten minutes was converted to cubic centimeters per minute per 100 c.c. of forearm. The volume of the segment of forearm was determined by the geometric method previously described.[7] All observations were made on the left forearm at 33.5 to 34.0° C. The rest periods between determinations of "reduced arm volume" (tissue volume with blood vessels collapsed) were four minutes, and from 3 to 6 determinations were required to obtain two successive readings differing by less than 1 c.c. The effective venous pressure in the occluding cuff on the upper arm was 50 cm. of water. The actual pressure in the cuff was higher by the amount of a correction factor determined for each observation, thus compensating for the hydrostatic pressure in the vertical forearm (see Landis and Gibbon[8]). The statistical constants were computed by standard formulas, as given by Treloar,[11] using corrections for smallness of samples.

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Observations

1. *Normal, Nonpregnant Controls.*—In 12 normal, nonpregnant women, ranging in age from 22 to 35 years, the mean rate of filtration of fluid into the tissues of the forearm was 0.111 ± 0.008 c.c. per minute per 100 c.c. of forearm. The range of individual values was from 0.088 to 0.167 c.c. per minute per 100 c.c. of forearm (Fig. 1, Table I). These values are similar to those found by White and Jones[9] in 16 normal subjects (9 females, 7 males) with comparable degrees of venous

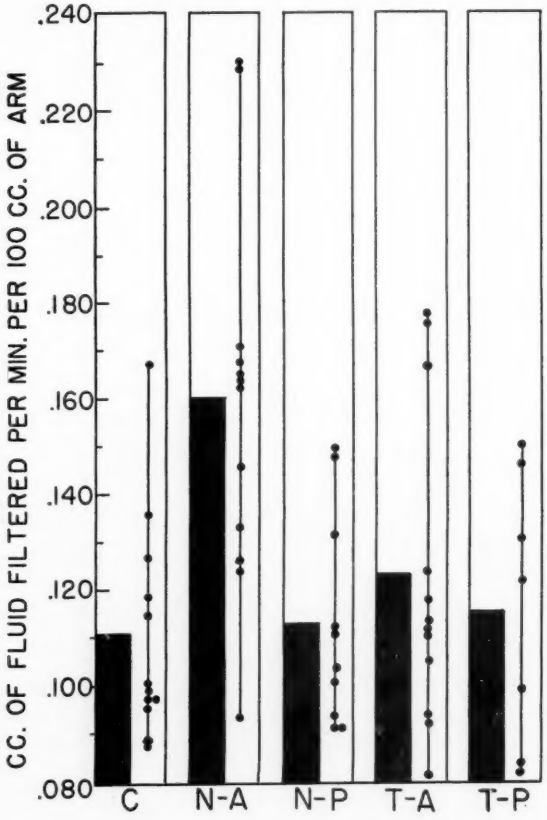

Fig. 1.—Rates of filtration in control subjects (Column C), normal pregnant women (*N-A*), normal post-partum patients (*N-P*), toxemic pregnancies ante partum (*T-A*) and post partum (*T-P*). The solid columns indicate the mean values, the perpendicular lines show the ranges, and the dots on these lines are the individual values.

congestion, and they compare favorably with the few observations of Krogh, Landis and Turner,[7] and those of Landis and Gibbon[8] at 50 cm. of venous pressure.

2. *Normally Pregnant Subjects.*—In 12 women observed late in normal gestations (thirty-second to fortieth week), the mean rate of filtration in the forearm was 0.160 ± 0.012 c.c. per minute per 100 c.c. of forearm, and the range was 0.094 to 0.230 c.c. (Fig. 1, Table I). Although many of the individual values for the pregnant women fall within the range of the nonpregnant rates, there is a statistically significant difference between the mean values of the two series (Table III).

TABLE I. RATES OF FILTRATION IN NORMAL WOMEN AND NORMALLY PREGNANT WOMEN AT 34° C.

SUBJECT	NORMAL WOMEN		NORMALLY PREGNANT, ANTE PARTUM			NORMALLY PREGNANT, POST PARTUM	
	AGE YEARS	FILTRATION RATE C.C. PER MINUTE PER 100 C.C. FOREARM	AGE YEARS	DURATION OF PREGNANCY WEEKS	FILTRATION RATE C.C. PER MIN. PER 100 C.C. FOREARM	POST-PARTUM DAY	FILTRATION RATE
1	25	0.088	23	40	0.094	–	–
2	27	0.089	21	36	0.124	10	0.104
3	29	0.096	29	39	0.126	10	0.132
4	26	0.098	18	37	0.133	–	–
5	35	0.098	25	37	0.145	70	0.112
6	27	0.099	32	40	0.163	13	0.101
7	26	0.100	25	32	0.164	8	0.092
8	29	0.115	20	40	0.165	13	0.149
9	27	0.119	28	39	0.167	45	0.094
10	22	0.127	30	37	0.171	51	0.092
11	24	0.136	20	39	0.229	13	0.111
12	22	0.167	20	39	0.230	10	0.147
Mean		0.111			0.160		0.113
Standard deviation		0.027			0.040		0.025
Standard error of mean		0.008			0.012		0.008

Ten of the normally pregnant patients were studied after delivery (8 to 70 days), at which time the mean filtration rate had dropped to 0.113 ± 0.008 c.c. per minute per 100 c.c. of forearm. This value does not differ significantly from that of the control subjects, but it is significantly lower than the mean value for the normally pregnant women (Table III).

3. *Pregnant Subjects With Toxemia.*—In 12 pregnant women with clinical diagnoses of pre-eclampsia, low reserve kidney (mild pre-eclampsia), or arteriolosclerotic toxemia, observed in the last six weeks of gestation, the mean filtration rate was 0.123 ± 0.010 c.c. per minute per 100 c.c. of forearm. The range was 0.082 to 0.177 c.c. (Fig. 1, Table II). The average value was not significantly different from that of the control subjects, but it was significantly *less* than that of the normally pregnant women (Table III).

After delivery (9 to 18 days) 7 of the toxemic women were restudied. At that time the average rate of filtration was 0.116 ± 0.012 c.c. per minute per 100 c.c. of forearm. This was not significantly different from (1) the ante-partum toxemic value, or (2) the rate for the nonpregnant controls, or (3) the post-partum rate for the normally pregnant women (Table III).

Discussion

These observations suggest that fluid filters through the capillary walls more readily in women late in normal pregnancies than it does in nonpregnant women. However, more individuals must be studied at all stages of gestation, with repeated observations in the same subjects, before the evidence will be conclusive. Whether or not the increased rate of filtration in normal pregnancy may be attributed to increased

TABLE II. RATES OF FILTRATION, ARTERIAL BLOOD PRESSURES AND OTHER PERTINENT DATA CONCERNING PATIENTS WITH TOXEMIAS OF PREGNANCY

SUBJECT	AGE YR.	CLINICAL DIAGNOSIS	HIGHEST ARTERIAL BLOOD PRESSURE MM. HG	LOWEST ARTERIAL BLOOD PRESSURE MM. HG	CLINICAL ESTIMATE OF EDEMA	PLASMA PROTEINS			URINARY ALBUMIN MAXIMUM	FILTRATION RATE			
						TOTAL GM./100 C.C.	ALBUMIN GM./100 C.C.	GLOBULIN GM./100 C.C.		WK. PREG.	RATE C.C./MIN./100 C.C. ARM	DAYS P.P.	RATE C.C./MIN. PER 100 C.C. ARM
1	20	Low reserve kidney	136/ 96	120/76	1+	6.5	4.0	2.1	0	40	0.082	–	–
2	21	Pre-eclampsia	152/102	100/60	None	–	–	–	3+	40	0.097	18	0.131
3	20	Pre-eclampsia	180/115	120/80	None	5.5	3.4	1.9	2+	36	0.098	8	0.082
4	20	Pre-eclampsia	150/110	125/80	None	4.7	2.8	1.6	Trace	40	0.105	9	0.150
5	23	Pre-eclampsia	166/115	125/75	1+	5.4	3.2	1.9	Trace	39	0.111	8	0.099
6	35	Low reserve kidney	146/ 95	110/70	1+	6.2	3.3	2.5	1+	41	0.112	–	–
7	23	Pre-eclampsia	150/105	105/70	None	–	–	–	Trace	41	0.113	10	0.084
8	26	Pre-eclampsia	175/110	130/80	1+	6.1	3.7	2.3	1+	35	0.118	9	0.122
9	40	Arteriolosclerotic toxemia	170/125	140/92	1+	5.8	3.8	1.8	Trace	36	0.124	–	–
10	31	Pre-eclampsia	180/120	115/80	None	5.9	3.3	2.3	Trace	32	0.167	9	0.146
11	16	Pre-eclampsia	176/130	114/70	None	5.6	3.8	1.8	1+	35	0.176	–	–
12	17	Pre-eclampsia	156/100	130/80	1+	6.3	3.7	2.6	Trace	40	0.177	–	–
Mean rate of filtration											0.123		0.116
Standard deviation											0.033		0.029
Standard error of mean											0.010		0.012

TABLE III. SIGNIFICANCE OF DIFFERENCES BETWEEN MEAN FILTRATION RATES FOR CONTROL, NORMALLY PREGNANT AND TOXEMIA SUBJECTS. RATE OF FILTRATION IN CUBIC CENTIMETERS PER MINUTE PER 100 C.C. OF FOREARM

GROUPS	DIFFERENCE BETWEEN MEANS	S. E. OF DIFF.	R(k)*	P*	SIGNIFICANT DIFFERENCE
Controls vs. normal pregnancy ante partum	0.048	0.014	3.43	0.0006	Yes
Controls vs. normal pregnancy post partum	0.002	0.011	0.18	0.8572	No
Controls vs. toxemic pregnancy ante partum	0.012	0.013	0.94	0.3524	No
Controls vs. toxemic pregnancy post partum	0.005	0.014	0.35	0.7339	No
Normal pregnancy ante partum vs. same, post partum	0.046	0.014	3.19	0.0014	Yes
Normal pregnancy ante partum vs. toxemic pregnancy, ante partum	0.036	0.016	2.31	0.0209	Yes
Normal pregnancy post partum vs. toxemic pregnancy, post partum	0.003	0.014	0.21	0.8330	No
Toxemic pregnancy ante partum vs. toxemic pregnancy post partum	0.007	0.016	0.45	0.6599	No

*R or (k), ratio of difference to its standard error. P, probability of the (k) magnitude being exceeded solely through errors of random sampling.

permeability of the capillary walls cannot, of course, be answered directly by these plethysmographic studies since the colloid osmotic pressure of the blood proteins was not considered in each case in establishing the venous congestion as it was, for example, by White and Jones.[9] They employed a congesting pressure 20 cm. above the colloid osmotic pressure, as determined from albumin and globulin levels by the formula of Wies and Peters.[12] The reliability of such formulas, however, is open to serious question.[12, 13] Furthermore, it has been estimated[1] that the average colloid osmotic pressure in normal pregnant women at term is about 28 cm. of water, whereas it was 32 cm. for the normal females in the control series of White and Jones.[9] If, then, the average congesting pressure in the present series of pregnant women had been 4 or 5 cm. lower to compensate for loss of protein, the rate of filtration would have been somewhat lower, but perhaps not significantly decreased. For example, Krogh, Landis and Turner found that a drop of 1 cm. of water in colloid osmotic pressure was accompanied by an increase in filtration rate ranging from 0.0027 to 0.0045 c.c. per minute per 100 c.c. of arm at temperatures around 28 to 29° C. While normal pregnancy is commonly accompanied by some lowering of plasma proteins, it has not been demonstrated that this is a major factor in the production of edema.[1, 2] In fact, Dieckmann[1] has pointed out that the greatest diuresis and improvement in edema of pregnancy occurs immediately post partum when the serum protein concentration is lowest.

In view of what is known about filtration into edematous tissues,[8] and in the light of present concepts of water storage in pregnancy, one would not expect to find an increased rate of filtration in normal pregnancy. The apparent greater ease with which fluid enters the tissues would

suggest a relative state of tissue dehydration. If there be increased permeability of the capillary wall, why is there not sufficient subclinical edema in the latter weeks of pregnancy to diminish the rate of further filtration of fluid? Possibly the stage is set, so far as the condition of the capillary wall is concerned, for the production of edema, but some additional factor is required to establish the edematous state. Could this factor be the hypothetical humoral agent of Weiss[2]? Unfortunately, these questions cannot be answered by investigations of the present sort.

The diminution in rate of filtration in patients with toxemia of pregnancy could have been predicted from what is known about filtration in the presence of edema.[8] Apparently, then, even the mildest form of toxemia (see detailed findings in Table II) is accompanied by a considerable degree of edema, although the latter may not be clinically demonstrable even in the lower extremities. All of the toxemia patients were relatively symptom-free at the time of determination of filtration rate although all still exhibited some elevation of arterial blood pressure. Were it possible to study a group of more severely ill subjects, with obvious pitting edema, one might expect considerably lower filtration rates, with subsequent rises in the post-partum period.

Further patients are being studied with a view to confirming the trends indicated here. The subjects must be chosen with some care so that uncoperative individuals will not invalidate the results by moving about during the determinations. It has been impossible to get many pregnant women to remain perfectly still in the supine position for periods of one to two hours. And this fact, as well as certain other considerations, makes it difficult to carry out such tedious physiologic observations on patients with severe degrees of pre-eclampsia or eclampsia.

Summary

Using the pressure plethysmograph at 34° C., the rate of movement of fluid through the capillary wall was studied with a congesting venous pressure of 50 cm. of water in the forearms of 12 normal women, 12 normally pregnant women near term, and 12 pregnant women near term with some form of toxemia. Seventeen of the pregnant patients also were studied post partum.

The mean rate of filtration for the normal controls was 0.111 ± 0.008 c.c. per minute per 100 c.c. of forearm. In the normally pregnant women it was significantly greater, being 0.160 ± 0.012 c.c. After delivery the rate dropped to the control level. The patients with toxemia had a mean rate of 0.123 ± 0.010 c.c. per minute per 100 c.c. of forearm, which was not statistically different from that of the controls, but significantly lower than that of the normally pregnant women. There was no appreciable change in the toxemic patients after delivery.

Conclusions

From observations in a small series of patients, it appears that the rate of filtration through the capillary wall, contrary to expectation, is somewhat increased over the normal in the latter weeks of pregnancy. This may be the result of an increase in the permeability of the capillary wall, although other factors must be considered, particularly the level of the colloid osmotic pressure and the state of tissue hydration. Patients with even mild toxemias of pregnancy appear to have sufficient edema (usually not clinically demonstrable) to interfere with filtration of fluid into the tissues. Toxemic patients with massive generalized edema might be expected to show marked diminution in the rate of filtration.

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The author cites several cases in which saturated saline solution was introduced into the amniotic fluid to initiate active labor at full term. In cases of fetal death, 40 to 80 c.c. were injected. If the fetus was viable, 20 to 40 c.c. were used. The interval between this procedure and initiation of active labor was from forty-five minutes to twenty-four hours. The author feels from results in this short series that the sodium ion has a stimulating effect on the myometrium, and perhaps the increased tension due to added fluid volume in the amniotic sac had a favorable effect in starting labor. In the discussion, mention was made of 2 cases of uterine tetany, which had followed the Aburel procedure in a series of 30 cases observed in Argentina.

R. J. Weissman.

A REPORT ON SEQUENTIAL ABORTION*

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THE causes and treatment of sequential abortion are an important problem in the general consideration of sterility. Approximately 18 per cent of all pregnancies end in miscarriage. When we add to this list the fetal deaths due to abnormalities, prematurity, etc., the fetal mortality is appallingly high. Therefore, this field of obstetrics probably offers the greatest opportunity for fetal salvage of any of the angles of preventive obstetrics. Present-day obstetric care is more inadequate in this respect than the routine prenatal and delivery problems that arise daily. This inadequacy is due to the inherent gaps in our knowledge of the mechanics of implantation of the fertilized ovum, the normal maintenance of growth, and the controlling factors in uterine quietude or expulsive uterine contractions. One method of approach to these clinical problems is the gradual addition to the literature by many observers of careful clinical records so that eventually sufficient material will be available for worth while conclusions.

Material

This report consists of the records of 28 such representative cases, the treatment they received, results obtained, and the impressions gained during their care. No definite conclusions can be drawn, but suggestions for further study may be indicated. As Table I indicates, only 31 completed their pregnancies and three as yet are undelivered gestations. These form the basis of our observations. However, an analysis of the 37 additional pregnancies which these 28 patients had had before they came under our observation, reveal essential details for the evaluation of the whole. In spite of the fact that 12 of these women came primarily for the treatment of long-continued periods of sterility, the sum total of 71 pregnancies is an index of average fertility

TABLE I

Total number of patients	28
Total number of pregnancies	71
Total number of pregnancies treated	31
Total number of pregnancies undelivered	3
Total number of term living babies	16
Total number of pregnancies lost	12
Total number of patients with previous sterility	12
One previous miscarriage	12
Two previous miscarriages	4
Three previous miscarriages	1
Four previous miscarriages	1

*Read at a Joint Meeting of the Chicago, St. Louis, and Kansas City Gynecological and Obstetrical Societies, in Chicago, Illinois, February 21, 1942.

of approximately 2 pregnancies per patient. One might reasonably expect that the factors of disturbed physiology operating in sterility might be responsible for an increased incidence of miscarriage or premature labor, especially since the sterility of 5 of these patients followed a previous miscarriage. In a large series of relatively sterile patients the recurrent factors causing abortion, as described by Malpas,[1] would probably be more frequent than in normal patients. Seventy-five per cent of these patients treated for sterility produced normal, living babies. Twelve of these patients had had 1 miscarriage and 4 of them had had 2. One patient had lost 3 pregnancies and 1 had lost 4.

Malpas has calculated that one out of each 100 patients will abort the second time due to recurrent or random causes, and that this equation will become almost constant after the third abortion. According to his calculations, after the third abortion, only about 27 out of each 100 pregnancies will produce living babies. In this series there were only three demonstrable abnormal factors as listed by this author, one multiple pregnancy, twins delivered at five months, and two fetal malformations. These malformations both occurred in babies delivered during the latter portion of the third trimester of pregnancy. No malformations were noted in the fetuses of the early pregnancies, although they undoubtedly occurred as has been shown by Heusser and Streeter[2] and many others. In most instances the fetal sac had been discarded by the patient before entering the hospital or no gross evidence of the fetus was found when curettage was performed. There was no evidence of the toxemias of pregnancy or nephritis in these women. All serologic tests were normal, and there were no severe degrees of anemia. These abortions all occurred in private patients of the better class so that dietary deficiencies and environmental factors should have been minimal. Additions of large quantities of vitamins, especially vitamin E, were given early in pregnancy in every case.

The term in weeks or months at which these 71 pregnancies terminated raises questions as yet unanswered.

TABLE II

Term of Pregnancies in Months											
MONTHS	2	2½	3	4	5	6	7	8	9	UNDELIVERED	TOTAL
No. Pts.	9	5	11		3	6		5	29	3	71
Early Abortions in Weeks											
WEEKS	7	8	9	10	11	12	13	14			TOTAL
No. Pts.	1	8	2	3	2	6		3			25
Total number of pregnancies delivering between 5 and 8 months											14
Total number of pregnancies delivering at term											29
Total number of pregnancies delivering between 7 and 14 weeks											25

It would seem, as has been previously observed many times, that spontaneous abortion is most likely to occur about the time when a menstrual period would have otherwise occurred. Rhythmic activity such as that causing the menstrual period would seem to be closely related. Hormonal determinations have indicated that decreased production of progestin may be responsible for sequential abortion. These investigations have also suggested that the production of progestin is taken over from the ovary by the placenta at about the fourth month

of gestation. We should therefore logically be able to stop progestin substitution therapy at the end of sixteen weeks of pregnancy. In this series of patients only three of the miscarriages occurred between the end of the third and beginning of the fifth month. On the other hand there were three premature labors at five months, 6 at six months, and 5 during the eighth month of gestation. Premature labors would indicate either increased irritability of, or tension in, the uterus or some fundamental weakness of the membranes themselves. Only 29 of the 68 already delivered patients reached full term. It is hard to reconcile the occurrence of two missed abortions, one at six months, with the above facts, except on the basis of random factors.

According to more recently suggested standards, dosage was often quite inadequate. This was especially true in the earlier cases treated. However, a few of these patients paid more for their medication than they did for either their hospital care or medical attention. The average course of treatment and dosage is shown below.

TABLE III. RESULTS IN PATIENTS WITH PREVIOUS STERILITY

1. 11 years sterility	Term living baby
2. 13 months sterility	Term living baby
3. 14 months sterility	5-month premature ruptured membranes
4. 4 years sterility	Term living baby
5. 9½ years sterility	Term living baby. Second pregnancy, 6 months premature
6. 20 months sterility	8 weeks miscarriage
7. 2 years sterility	8 months malformation. Death 10 hours
8. 14 years sterility	7 months premature separation placenta
9. 15 months sterility	Full-term living baby
10. 4 years sterility	Full-term living baby
11. 10 years sterility	Full-term living baby
12. 4 years sterility	Full-term living baby

TOTAL NUMBER OF PATIENTS TREATED WITH			
PROLUTON	PROLUTON AND PROGESTEROL OR PRANON	PRANON	PROGESTEROL
19	4	2	6

FETAL RESULTS IN VARIOUS GROUPS TREATED WITH			
PROLUTON		PROLUTON WITH PRANON OR PROGESTEROL	
LIVING BABY	FETAL DEATH	LIVING BABY	FETAL DEATH
15 (1—L, 1—U)	6 (2—*, 1—O)	3 (1—L)	3
PROGESTEROL		PRANON	
LIVING BABY	FETAL DEATH	LIVING BABY	FETAL DEATH
1	3	1	1

*Fetal malformations. Born alive.
O, Missed abortion.
L, Delivered full-term after this report was completed.
U, Undelivered but near term.

It would seem from the above results if progestin is of help in the treatment of sequential abortion hypodermic administration is to be preferred. The number of patients treated by medication given orally or in combination with injection is too small to comment upon except that they were very disappointing.

A résumé of the case histories is appended.

Abortion Case Histories

CASE 1.—R. L., 1937, aged 41 years. Last menstrual period, May 25, 1939. Previous miscarriage, 12 weeks. Eleven years' sterility. First examination, June 30, 1939. *Pelvic Findings:* Uterus slightly enlarged. Zondek plus, July 3. *Medication:* Thyroid gr. ½ daily, wheat germ oil min. 20 b.i.d.; proluton 5 mg. twice weekly. Bed rest. *Bleeding* began July 21. During next two months 3 periods of bleeding, as much or more than a menstrual period. *Treatment:* Each time by proluton ampoules, one 5 mg. b.i.d. *Delivered:* February 10, 1940. Weight of infant, 6 pounds 7½ ounces.

CASE 2.—B. L., aged 20 years, 10 months' sterility. Last menstrual period, Oct. 21, 1939. Treated 13 additional months for sterility. Aborted 3½ months. No treatment. *Treatment:* for sterility began again Nov. 7, 1938. Thyroid gr. 1 daily until six months, wheat germ oil min. 20 b.i.d., complete bed rest. Proluton 5 mg. twice weekly. Slight bleeding Jan. 4, 1940. Proluton 10 mg. twice daily for 4 days, then 1 mg. daily five days. *Delivered:* July 20, 1940. Weight of infant 9 pounds 6 ounces. This patient is now in the eighth month of another pregnancy. False labor of eight hours' duration occurred at twenty-eight weeks. Given proluton 10 mg.

CASE 3.—H. P. F., aged 31 years. Last menstrual period Aug. 26, 1939. Previous miscarriages; first husband, twins at 5 months; second husband, at three months. *Treatment:* Thyroid gr. ½ daily, wheat germ oil min. 20 b.i.d. Bed rest. Proluton ampoule 1, 1 mg. twice weekly. Two periods of bleeding October 4 to 8, and October 26 to 29. Proluton ampoule 1, 10 mg. b.i.d. during bleeding and for three days after cessation. *Delivered:* Cesarean section June 9, 1940. Weight of infant 6 pounds 5 ounces. Last menstrual period July 23, 1941. Slight bleeding three days beginning Sept. 4. *Treatment:* Progesterol 5 mg. t.i.d. for six days and then 1 daily for seven days. Bed red. Felt life Nov. 18, 1941. Pregnancy progressing normally.

CASE 4.—E. M., aged 28 years. Last menstrual period May 11, 1940. Previous miscarriages: 1938: 10 weeks term. Two previous full-term pregnancies, last being July 1, 1934. Slight bleeding January 8 and 9. *Treatment:* Proluton ampoule 1, 1 mg. daily, then twice weekly. Bleeding 7 days beginning July 5, 1940. Proluton ampoule 1, 1 mg. daily, wheat germ oil 20 min. b.i.d. Bed rest. *Delivered:* Jan. 30, 1941. Weight of infant 7 pounds 10 ounces.

CASE 5.—B. C., aged 25 years. Last menstrual period Feb. 9, 1941. Previous miscarriage: One 11 weeks from term 6 months ago. Term pregnancies: one 2 years old. Moderate bleeding began April 7, 1941, lasted 7 days. *Treatment:* Progesterol 5 mg. t.i.d. for three days, 2 mg. daily for three days. Progesterol 1 mg. daily, for three days. Bleeding began again April 15, 1941, and above routine repeated. Bleeding stopped April 18. Bed rest, wheat germ oil min. 20 b.i.d. Thyroid gr. ½ daily. *Delivered:* Oct. 24, 1941. Weight of infant 6 pounds 8 ounces.

CASE 6.—Mrs. J. W. M., aged 34 years. Last menstrual period June 1, 1939. Miscarriages, 2. One 10 years ago at 11 weeks term. One 1 year ago at 9 weeks term. Examined first July 28, 1939. *Treatment:* Placed on proluton 5 gr. t.i.d., thyroid gr. ½ b.i.d., wheat germ oil min. 20, b.i.d., relative bed rest. Began bleeding moderately Aug. 7, 1941. Proluton 5 mg. 1 ampoule t.i.d. for three days. Bleeding ceased in forty-eight hours. Proluton ampoule one, 5 mg. continued for 7 days. Bleeding recurred and above routine repeated. Bed rest, continued thyroid, wheat germ oil. *Delivered:* March 12, 1940. Weight of infant 7 pounds 8 ounces.

CASE 7.—C. G., aged 36 years. Miscarriages, one 8 weeks term. No treatment. Last menstrual period approximately March 26, 1938. Bleeding began June 26, 1938, quite profuse. *Treatment:* Proluton ampoule one, 5 mg. t.i.d. for four days. Bleeding ceased in 3 days. Proluton ampoule 2, 5 mg. for two days and then once each day for 1 week. Bed rest, wheat germ oil min. 20 b.i.d. Thyroid gr. ½ daily. *Delivered:* Dec. 26, 1938. Weight of baby 8 pounds.

CASE 8.—D. H., aged 39 years. Miscarriage, one. Nine-week term. No treatment. Previous pregnancy: one normal child, Dec. 29, 1930. Second, 1931 by cesarean section. Ectopic vesicae, repair. Survival. 7 pounds 4 ounces. Last menstrual period Aug. 24, 1939. Bleeding began Nov. 6, 1939. *Treatment:* Proluton ampoule 1, 5 mg. t.i.d. for three days. Bleeding decreased. Ampoule 2, 5 mg. b.i.d. two days. Brownish discharge 9 days. Proluton 1 ampoule 5 mg. daily 12 days. Bed rest. Thyroid gr. ½ b.i.d., wheat germ oil min. 20, b.i.d. *Delivered:* May 14, 1940. Nasal septum absent, cleft palate, brain one-half normal size. Subepicardial hemorrhage, horseshoe kidney. Marked cyanosis after delivery. Death in six hours.

CASE 9.—L. H., aged 33 years. Miscarriages, 2. One 4 years ago, 3 mo. term. One miscarriage 7 years ago, 3½ mo. term. Treated 13 months for sterility. Last menstrual period Feb. 12, 1940. Examined first on March 12. Zondek plus on March 15. *Treatment:* Complete bed rest. Thyroid gr. ½ daily. Proluton ampoule of 1 mg. twice daily. First bleeding slight, on April 10, 1939. Proluton ampoule 1, 5 mg. b.i.d. for 3 days, then ampoule 1, 1 mg. daily for 7 days, followed by ampoule of 1 mg. twice daily. Spotting again May 5. Slight bleeding June 13, 1940. *Delivered:* Aborted June 18, 1940. Infant not weighed.

CASE 10.—K. D. Miscarriages, 3. Two at 6 months and 1 at 5½ months, 1934. Last menstrual period Feb. 27, 1938. Basal metabolic rate minus 14 per cent. *Treatment:* Thyroid gr. ½ b.i.d. Proluton ampoule 1, 1 mg. one to two times weekly. Wheat germ oil min. 15 b.i.d. Continued until thirty-sixth week. Absolute bed rest. *Delivered:* Nov. 20, 1938. Weight of infant 8 pounds 1 ounce.

CASE 11.—M. B., aged 38 years. Miscarriages 2. In 1933 full term, normal; 1937 miscarriage at 2 months, also 1938 at 2 months. Treatment for sterility included removal of cervical polyp at 6 months. Last menstrual period May 1, 1940. *Treatment:* Bed rest, thyroid gr. ½ daily. Wheat germ oil min. 20 b.i.d. Proluton ampoule 1, 5 mg. twice weekly. *Delivered:* Dec. 24, 1940. Weight of infant 5 pounds 6 ounces. Complete atresia second portion duodenum. Lived 10 hours.

CASE 12.—E. H. Normal pregnancy, Dec. 24, 1935. Miscarriages, 4. First, June 25, 1937, at three months term. Second, Jan. 18, 1938, at 10 weeks term. Third pregnancy, last menstrual period, May 20, 1941. Vaginal bleeding began July 10, 1941. *Treatment:* Bed rest. Thyroid gr. ½. Proluton ampoule 1, 5 mg. b.i.d. Pranon 5 mg. daily. Bleeding stopped. Began July 28, 1941. Proluton ampoule 1, 5 mg. daily. Pranon 5 mg. b.i.d. Aborted July 31, 1941. Fourth miscarriage. Last menstrual period Sept. 22, 1941. Zondek positive November 6, 1941. *Treatment:* Complete bed rest. Thyroid gr. 1 daily. Proluton 5 mg. daily. Spotting began Nov. 27, 1941. Proluton 5 mg. b.i.d. Progesterol 5 mg. t.i.d. Aborted Dec. 17, 1941. She is again pregnant and due to deliver Dec. 19, 1942. Proluton 10 mg. daily given from 5 to 30 weeks of gestation.

Cases With One Miscarriage

CASE 13.—G. F., aged 30 years, 1 miscarriage, 2 years three months ago. One full-term pregnancy; child now 4 years old. Last menstrual period July 24, 1939. First seen Sept. 8, 1939. Bleeding slight November 13, 14, and 15. *Treatment:*

Proluton ampoule of 1 mg. daily, for 5 days, then each 2 days for 5 days. Bed rest. Thyroid gr. ½ daily. Remainder of pregnancy uneventful. *Delivered:* April 24, 1940. Weight of infant 9 pounds 2 ounces.

CASE 14.—V. D., aged 29 years. First pregnancy; last menstrual period Jan. 30, 1939. Spotting March 3. *Treatment:* Proluton ampoule 1, 1 mg. daily for 3 days, ampoule 1 each 3 days for 7 days. Thyroid gr. 1 daily. Basal metabolic rate minus 20. *Delivered:* Nov. 13, 1939. Weight of infant 6 pounds 8 ounces. Second pregnancy; last menstrual period Nov. 18, 1940. Zondek positive, Jan. 8, 1941. Bleeding began February 15, 16, and 17, 1941. *Treatment:* Proluton ampoule 1, 1 mg. b.i.d. for 4 days, then ampoule 1 daily for 3 days, then ampoule 1 each 2 days for 5 days. Examined March 28, 1941. Uterus only 7 to 8 weeks size. Missed abortion.

CASE 15.—S. G., aged 28 years. One miscarriage at 4 weeks, 1936. Last menstrual period Jan. 28, 1940. Moderate bleeding began March 18, 1940. *Treatment:* Bed rest. Thyroid gr. 1 daily. Pranon 5 mg. b.i.d. Bleeding and pranon continued for 10 days. Pranon gradually reduced to 1 each 3 days until March 24. Continued until June 4, 1940. *Delivered:* Nov. 3, 1940. Weight of infant 7 pounds 11 ounces.

CASE 16.—H. B., 1 pregnancy, 3 years ago. Present pregnancy: last menstrual period June 22, 1939. Bleeding August 4, 5, and 6. *Treatment:* Wheat germ oil min. 20, b.i.d. Bed rest. Thyroid gr. ½ daily. Proluton ampoule 1, mg. 5 for 3 days, then ampoule 1, mg. 1 daily for 3 days. Bleeding September 5 and 6. Above treatment repeated. *Delivered:* March 23, 1940. Weight of infant 7 pounds 11 ounces.

CASE 17.—H. K., aged 29 years, 1 miscarriage of 8 weeks, Nov. 14, 1939. Last menstrual period Jan. 31, 1940. Examined first April 1, 1940. Uterus 8 weeks size. *Treatment:* Proluton ampoule 1, mg. 1 daily. Bed rest. Thyroid gr. ½ daily. Wheat germ oil min. 20 b.i.d. Bleeding began profusely April 16, 17, 18, 1940. Proluton 5 mg. b.i.d. for 5 days, then 1 each day for 3 days, then 1 ampoule 1 mg. daily. Continued to fifth month. Pranon 5 mg. 3 times a week to sixth month. *Delivered:* Oct. 25, 1940. Weight of infant 5 pounds 1 ounce.

CASE 18.—H. T. One full-term pregnancy; delivered Aug. 25, 1933. Last miscarriage Nov. 8, 1935 at 8 weeks term. Last menstrual period June 7, 1936. Patient fell one-half floor in elevator Jan. 19, 1937. Pains began Feb. 4, 1937. Bleeding irregular until March 11, 1937. Pains began again. Nothing stopped pains except proluton ampoule 1, 1 mg. t.i.d. A similar period of pains of 12 hours' duration on March 15, 1937. *Treatment:* Proluton ampoule 1, 1 mg. every 4 hours. Pains ceased. *Delivered:* March 21, 1937. Weight of infant 8 pounds.

CASE 19.—M. H., aged 39 years, 9½ years' sterility. Treated 2 years. Full-term delivery Dec. 8, 1937. Birth weight 7 pounds 11 ounces. One 6 months premature. Proluton 10 mg. given daily for 1 week preceding premature delivery due to very painful uterine contractions.

CASE 20.—A. K., 10 months' retained fetus. Uterus stopped growing at about 4 months. Curettement advised June 5, 1938. Curetted July 14, 1938. No fetus. Sclerotic placental tissue. Patient, aged 24 years. Last menstrual period April 25, 1939. Moderate bleeding. June 20, 21, and 22. *Treatment:* Proluton ampoule 1, 5 mg. b.i.d. for 5 days. Ampoule 1, 5 mg. daily for 3 days. Ampoule 1, 1 mg. each 2 days until feeling fetal life Sept. 12. Bed rest. Thyroid gr. 1 daily. Wheat germ oil min. 22 b.i.d. *Delivered:* Jan. 26, 1940. Weight of infant 6 pounds 1 ounce. Patient had 4 somewhat profuse but normal menstrual periods beginning late in April. Entered hospital during fifth menstrual period after first week of very

profuse bleeding. During the following 16 days the patient was curetted twice and packed once for profuse bleeding. Hemoglobin and red count were 40 per cent and 2,800,000. Seven thousand seven hundred cubic centimeters of blood were given during this time. Vaginal hysterectomy Nov. 23, 1940. No evidence fetal tissue or other abnormalities on microscopic examination of tissue taken from many areas in the uterine wall. Large vacuoles found in intimal cells of large blood vessels.

Sterility

CASE 21.—D. B., married 11 years. Never pregnant. Treated 15 months. Last menstrual period June 2, 1940. Zondek positive July 19, 1940. *Treatment:* Bed rest. Thyroid gr. ½ b.i.d. Wheat germ oil, min. 20 b.i.d., pranon 5 mg. each 2 days begun August 8. Bleeding began August 14, 15, and 16. Proluton ampoule 1, 5 mg. b.i.d. for 5 days then ampoule 1, mg. 1 each 3 days until Nov. 8, 1940. *Delivered:* March 22, 1941. Weight of infant 6 pounds 10 ounces.

CASE 22.—H. S., aged 36 years. Married 14 years. Treated 3½ years. Last menstrual period May 3, 1941. Bloody discharge began July 3, 1941. *Treatment:* Given progesterol daily. Bleeding continued 2 weeks. One week later progesterol 3 times each week. Felt life Oct. 14, 1941. Rupture membranes, short cord, separation placenta during labor. *Delivered:* Jan. 2, 1942. Infant not weighed. Lived 6 hours.

CASE 23.—E. A., aged 34 years, 20 months sterility treated for 6 months. Zondek positive Dec. 29, 1941. Last menstrual period Nov. 23, 1941. Began bleeding Dec. 24, 194[illegible]. *Treatment:* Bed rest. Thyroid gr. ½ b.i.d. Wheat germ oil 20 min. b.i.d. Progesterol 5 mg. t.i.d. Bleeding lasted 1½ weeks. Progesterol cut to 2 each day. Began spotting again Jan. 19, 1942. Bleeding began Jan. 24, 1942. Curetted Jan. 29, 1942. She is now in her eighth month of pregnancy. Bleeding began 3½ months for 4 days. Proluton 10 mg. daily given.

CASE 24.—C. S. One full term 4 years. One miscarriage. Last menstrual period Aug. 4, 1940. Bleeding began Nov. 8, 1940. *Treatment:* Progesterol 5 mg. 3 times daily. Bed rest. Wheat germ oil. Proluton 1 mg. twice each week. Two doses. *Aborted:* Nov. 11, 1940. Last menstrual period Dec. 6, 1941. Bleeding of 3 days' duration slight, Jan. 3, 1942. *Treatment:* Bed rest. Zondek positive Jan. 5, 1942. Relative bed rest. Pranon 5 mg. daily. Slight bleeding Feb. 7, 1942. Cramps. Proluton 10 mg. daily. Vitamins E and C. Bed rest. Progressing normally. Felt life March 27, 1942.

CASE 25.—V. W., aged 35 years, 8 months delivery May 2, 1937. Erythroblastosis. Last menstrual period June 20, 1935. Bleeding August 14 to 19. *Treatment:* Proluton ampule 1, 1 unit daily for 8 days, then ampoule 1, 1 unit twice each week. Thyroid gr. ½ daily. Bed rest. Bleeding began again Dec. 20, 1935. Proluton ampoule 1, 1 unit each 2 days. Bed rest until March 22, 1936. *Delivered:* March 22, 1936. Weight of infant 7 pounds 2 ounces.

CASE 26.—W. J. L. Child 4 years ago. Living and well. Child 2 years ago. Died intrauterine, retained 10 days in uterus. Last menstrual period Dec. 3, 1938. Felt life April 19, 1939. June 12 no motion, no heart tones. *Delivered:* Aug. 2, 1939. Basal metabolic rate minus 8. *Treatment:* Thyroid 1 gr. daily. Wheat germ 20 drops daily. Last menstrual period May 20, 1940. Above continued. Pranon 5 mg., 3 times each week. *Delivered:* Dec. 25, 1940.

CASE 27.—L. C., aged 23 years. No previous pregnancies. Married 16 months. Mitral stenosis. Last menstrual period Nov. 16, 1941. Bleeding began Jan. 12,

1942. *Treatment:* Progesterol 5 min. 3 times daily. Bed rest. Wheat germ oil min. 20 daily. Bleeding began Jan. 19, 1942. Curetted on Jan. 20, 1942.

CASE 28.—C. H., aged 32 years. Two full-term pregnancies. Last menstrual period Aug. 8, 1941. Spotting began Nov. 3, 1941. Seen first Nov. 10, 1941. *Treatment:* Bed rest, thyroid gr. ½ b.i.d. Wheat germ oil min. 20 daily. Proluton 1 ampoule 5 mg. given in office. Progesterol 5 mg. 3 times daily. Bleeding stopped Nov. 18, 1941. Pregnancy continuing normally.

Summary

Average treatment: Complete bed rest during active bleeding or, as soon as pregnancy was diagnosed in the patient of prolonged sterility, or who had had previous miscarriage.

Continued bed rest for 2 weeks or occasionally to 10 weeks.

Thyroid grain ½ to 1 daily.

Wheat germ oil min. 20, or ethynl acetate 3 mg. each day.

Proluton 1 to 10 mg. 1 to 2 times each day during bleeding, and decreased to 1 mg. twice each week.

Pranon 5 to 10 mg. each day during active bleeding, decreased to each two days.

Progesterol 5 to 10 mg. each day.

No definite conclusion can be drawn from this small group of patients. However, certain impressions may be gained.

1. If progesterone therapy is of value in habitual abortion, it should be extended to the period of viability.

2. That late premature rupture of the membranes suggests estrone predominance.

3. That larger doses of progesterone be used and the preferable route of administration seems to be parenterally.

In the group delivering between the fifth and the eighth month the following fetal conditions were found.

1. One with absence of nasal septum, cleft palate, horseshoe kidney, and small brain.

2. One with complete atresia of second portion of duodenum.

3. One with probable erythroblastosis.

4. Three with premature rupture of the membranes.

5. Two missed abortions, one at five months and another at two months.

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THE FLUIDITY OF MENSTRUAL BLOOD, A PROTEOLYTIC EFFECT*

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ALTHOUGH the presence of fluid blood in the menstrual discharge of normal women has long been known, the subject has not been examined until recently with modern coagulation methods.

It is generally agreed that the coagulation of blood occurs because of the interaction of two proteins, thrombin and fibrinogen. A working mechanism of coagulation, accepted by many investigators, may be summarized as follows:

Prothrombin + Ca^{++} + Thromboplastin → Thrombin
Fibrinogen + Thrombin → Fibrin.

During menstruation the peripheral blood coagulates normally.[2-4] The menstrual fluid does not contain fibrinogen,[1, 2, 6, 8] thrombin,[1, 2, 6, 7] prothrombin,[1, 2] or anticoagulants.[1, 2] The calcium content has been stated to be normal[2, 3, 6] and the fluid contains an abundance of the factor which promotes clotting of hemophilic blood.[2]

The theory is not new that menstrual blood is fluid because of a lytic agent which dissolves the clot after it has formed in the uterine glands or cavity. Halban and Frankl[4] found that strips of mucosa in the premenstrual stage digest protein; this proteolytic ferment is absent in the postmenstrual stage. Frankl and Aschner[5] found that premenstrual uterine epithelium liberated important amounts of tyrosin crystals on incubation with peptone (seidenpepton) in a weakly alkaline solution. Rona and Waldbauer[12] observed that nonprotein N and amino-N of menstrual blood from the uterus were higher than in circulating blood, attributing the increase to proteolysis. Glueck and Mirsky,[1] and Lozner, Taylor and Taylor[2] concluded that menstrual fluid contains blood which has previously been clotted, the clot being dissolved by some hypothetical lytic agent. Whitehouse[8] obtained evidence for what he considered to be a specific fibrinolysin: mixing menstrual blood with venous blood in equal amounts, complete resolution of the clot occurred in from twelve to twenty-four hours in 12 cases, with partial resolution in 6 tests. Kross[10] mixed fluid from the uterus of rats with venous blood and observed that the blood clots were dissolved within a short time. He[11] also found that hematocolpos fluid from a young woman readily liquefied clots from venous blood in three hours.

Materials and Methods

Menstrual fluid was obtained on the first or second day of catamenia from 38 women by the use of a rubber vaginal diaphragm. The blood

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was collected for three to six hours and tested immediately; in most cases a pinch of sulfathiazole powder (about 50 mg.) was placed in the cup to inhibit bacterial action. Peripheral blood was obtained from the patient, other persons and rabbits; potassium oxalate, 20 mg., was used as an anticoagulant for blood, 10 c.c. and the plasma was diluted 1:4 with saline. Testing for fibrinolysis was carried out by mixing the diluted oxalated plasma, 1 c.c., with menstrual blood 0.5 c.c., either undiluted or diluted with saline to this amount and adding calcium chloride (0.25 per cent), 0.25 c.c. In specified instances no calcium was added. The tubes were placed in a water bath at 37° C. and the time of clotting and of lysis were noted.

In 12 rats under ether anesthesia, the uterine cornua were ligated with silk. Stillbestrol, 0.1 mg. dissolved in olive oil, was injected twice weekly and after two weeks the abdomen was reopened and the uterine secretion aspirated.

Purified fibrinogen, thrombin, and thromboplastin were prepared from beef plasma and lung by the method of Smith, Warner, and Brinkhous[20] and prothrombin by the technique of Seegers and colleagues.[21]

Trypsin was determined by the method of Anson[16] and the results were expressed in units of Kolm, Shay and Gershon-Cohen:[17] one unit of trypsin representing the liberation of chromogen equivalent to that produced by trypsin, 1 mg. in one minute per 100 c.c., under stated conditions from denatured hemoglobin. Citrate determinations were made by the method of Pucher, Sherman, and Vickery.[18] Acid and alkaline phosphatase were determined by the King and Armstrong method.[19, 23]

Results

Clotting Time and Fibrinolysis With Menstrual Fluid.—Determination was made of the coagulation time of 19 specimens of recalcified oxalated peripheral blood, 1 c.c., mixed with menstrual fluid, 0.5 c.c. The clotting time was the same as the controls in four instances, slightly lessened in 12, and slightly prolonged in 3 cases. The most rapid clotting occurred in two and one-half minutes, and the most prolonged time was twelve minutes; the average clotting time of controls in which saline replaced menstrual blood was six minutes.

The effect of menstrual blood on subsequent lysis of the clot is shown in Tables I and II.

Fibrinogenolysis.—The destruction of plasma fibrinogen by menstrual blood was slight. The effect was determined in 12 cases by incubating menstrual fluid, 0.5 c.c., with oxalated peripheral blood, 1 c.c., without additional calcium for two to six hours when calcium chloride was added. All specimens clotted on adding calcium ions in nearly the same time as did the control plasmas containing menstrual fluid where calcium was added immediately after mixing.

Spontaneous Induction of Clotting.—In two tests of twelve, menstrual blood, 0.5 c.c., within one hour caused clotting of oxalated human plasma without added calcium; smaller amounts were ineffective. In the remaining instances, the plasma remained fluid for two to six hours when clotting occurred on adding calcium.

Menstrual blood, 0.5 c.c., always clotted oxalated rabbit plasma, 1 c.c., within one to fifteen minutes without adding calcium. In eight tests, menstrual blood did not induce clotting with less than 0.5 c.c. amounts; in one instance 0.1 c.c. was effective and in one test as little menstrual blood as 0.012 c.c. caused clotting in twelve hours. Spontaneous clot-

TABLE I. FIBRINOLYSIS OF HUMAN OXALATED PLASMA BY MENSTRUAL FLUID

Plasma, 0.2 c.c. + saline 0.8 c.c. + menstrual fluid, 0.5 c.c. either undiluted or diluted to 0.5 c.c. + $CaCl_2$ 0.25%, 0.25 c.c.	
Incubation at 37° C.	Dissolution in 18 hours or less
Number of tests: 38	
Complete dissolution	25
Partial dissolution	11
No dissolution	2
Time of solution of clots.	
½—2 hours	11
2—5 hours	6
5—18 hours	8
Amount of menstrual blood causing dissolution: 19 tests.	
No less than 0.5 c.c.	1
No less than 0.1 c.c.	4
No less than 0.05 c.c.	8
No less than 0.05 c.c.	6

ting did not occur in the control rabbit plasmas with saline replacing menstrual blood. Added anticoagulant, potassium oxalate, 8 mg. in 1 c.c. of plasma did not inhibit the clotting effect of menstrual blood.

Dialysis of menstrual blood in a cellulose bag for two days against running tap water still permitted it to induce spontaneous clotting of rabbit plasma. Menstrual blood, 0.5 c.c. did not clot purified beef fibrinogen; after incubation for three hours the addition of thrombin produced quick firm clots. Menstrual blood did not cause clotting of beef plasma from which prothrombin had been adsorbed by colloid Mg $(OH)_2$.

The Content of Trypsin and the Phosphatases in Menstrual Blood.—Trypsin was determined on 19 menstrual fluids by the method of Anson[16] using denatured hemoglobin as substrate and the results were expressed in the units of Kolm and others.[17] In two cases no trypsin was demonstrated; in seventeen determinations the results ranged from 0.1 to 1.6 units per 100 c.c. The average was 0.63 units.

The trypsin content of rat uterine fluid varied from 0.25 to 1.5 units, the median value was 0.4 units.

Acid phosphatase values in eight tests ranged from 20 to 55.5 King and Armstrong units per 100 c.c. of whole blood; alkaline phosphatases varied from 6.75 units to 23 units. The phosphatases of peripheral blood were not abnormal.[23]

Proteolytic Capacity of Rat, Rabbit, and Dog Uterine Fluid.—The uterine fluid of the rat rapidly lysed human blood (Table II); in six tests, plasma, 1 c.c., was completely lysed in one-half to three hours by amounts as low as 0.002 c.c. Human plasma was lysed more effectively and quicker than rat plasma.

Rabbit uterine fluid added in equal parts to human blood produced only slight lysis in eighteen hours.

The uterine fluid of dogs prolonged the clotting times of human and dog blood and exhibited no lytic action in any concentration in eighteen hours. Thirty-one tests were made on uterine fluid of five dogs; fresh blood without anticoagulants, was added to equal volumes of undiluted uterine fluid. The clotting time varied from fifteen to forty minutes. When saline replaced uterine fluid, the average clotting time of human blood was six minutes and of dog blood, three minutes.

TABLE II. EFFECT OF MENSTRUAL FLUID AND UTERINE SECRETIONS OF ANIMALS ON FIBRINOLYSIS OF HUMAN PLASMA

Oxalated plasma, 0.2 c.c. + saline 0.8 c.c. + secretion, 0.5 c.c., undiluted or diluted with saline + $CaCl_2$ (0.25%) 0.25 c.c.

Time of lysis in hours

NATURE OF FLUID	AMOUNT OF SECRETION IN TEST*					
	0.5	0.1	0.05	0.025	0.016	0.0125
Menstrual fluid	L 1 hour	L 3 hours	L 5 hours	L 18 hours	I 18 hours	0 18 hours
Menstrual fluid	L 1 hour	L 1 hour	L 4 hours	L 4 hours	I 8 hours	0 18 hours
Uterine secretion, rat	L ½ hour	L ½ hour	L ½ hour	L ½ hour	L ½ hour	L ½ hour
Uterine secretion, rabbit	I 18 hours	0 18 hours	0 18 hours	0 18 hours	—	—
Uterine secretion, dog	0 18 hours	0 18 hours	0 18 hours	0 18 hours	—	—
Prostatic fluid, man†	—	L 18 hours	L 18 hours	L 18 hours	L 18 hours	L 18 hours
Prostatic fluid, dog‡	—	L 7 hours	L 18 hours	0 18 hours	0 18 hours	—

*L, complete lysis; I, partial lysis; 0, no lysis.
†Data of Huggins and Neal.[13]
‡Data of Huggins and Vail.[15]

Lytic Activity of Endometrium.—Saline extracts of endometrium ground with sand were tested against equal volumes of blood. The tissue was obtained from uteri at hysterectomy (Table III). As controls, ground fresh prostate gland from 12 men and thyroid glands from 5 persons were used. Only in the larger concentrations was lysis observed, and excepting one case, there was less lytic activity in endometrial extracts than in the controls.

TABLE III. LYTIC ACTIVITY OF SALINE EXTRACTS OF ENDOMETRIUM AND OTHER TISSUES ON WHOLE BLOOD

TISSUE 1 GM. GROUND WITH SAND IN SALINE, 3 C.C., AND EXTRACTED 24 HOURS AT 4° C.

TEST: HUMAN VENOUS BLOOD, 1 C.C., + 1 C.C. OF SALINE EXTRACT, UNDILUTED OR DILUTED TO 1 C.C.

EXTENT OF LYSIS AT 18 HOURS

TISSUE	AMOUNT OF EXTRACTION IN TEST* C.C.					DIAGNOSIS
	1	0.2	0.1	0.05	0.03	
Endometrium	L	0	0	0	0	Multiple leiomyomas. Residual chronic salpingitis. Hemorrhagic follicles of ovary
Endometrium	L	L	L	0	0	Multiple leiomyomas of corpus. Simple cyst of right ovary. Minute par-ovarian cysts
Endometrium	L	I	0	0	0	Normal corpus and cervix. Multiple follicle cysts of ovary
Endometrium	L	0	0	0	0	Normal uterus. Fallopian tube normal. Bilateral hemorrhagic cysts
Endometrium	L	I	0	0	0	Normal corpus and cervix. Mild salpingitis. Probable luteoma of ovary
Prostate	L	L	I	0	0	Benign hypertrophy
Prostate	L	L	L	0	0	Benign hypertrophy
Prostate	L	L	0	0	0	Benign hypertrophy
Prostate	L	L	0	0	0	Benign hypertrophy
Prostate	L	L	0	0	0	Benign hypertrophy
Thyroid	L	L	L	0	0	Hyperthyroidism
Thyroid	L	L	I	0	0	Hyperthyroidism
Thyroid	0	0	0	0	0	Hyperthyroidism

*L, complete lysis; I, incomplete lysis; 0, no lysis.

Citrate Content of Human Uterine Blood.—The secretion of the human prostate is so rich in citric acid that it prevents the coagulation of blood.[13] In 6 cases, menstrual blood was tested for citrate; the values were between 1.1 and 5 mg. of citric acid per 100 c.c. Normal peripheral venous blood of 24 adults contained 0.9 to 2.6 mg. per cent.

Discussion

Proteolytic activity as determined by the dissolution of fibrin was observed in 36 of 38 menstrual fluids tested. Fibrinolysis was always greater in specimens collected for a short time and promptly tested than in older samples. All fresh specimens of menstrual blood exhibited fibrinolytic activity which was absent only in those cases where putrefaction had occurred.

The proteolytic activity of menstrual blood against fibrin is weaker than the secretions of the adult prostate gland of dog and man, which in the latter case is particularly strong (Table II). Our observations on the uterine fluid of rats confirm the findings of Kross[10] that strong fibrinolytic activity is present in rat uterine fluid; there is less proteolytic activity in menstrual fluid than in the rat secretion. The rat fluid was opalescent and without obvious signs of infection and did not readily undergo putrefaction, while menstrual blood despite the addition of sulfathiazole tended to spoil. It is of interest that the trypsin content of the exceedingly active rat secretion was no higher by the method used than the trypsin of menstrual blood.

Concerning the relatively mild action of menstrual blood in dissolving fibrin the possibility of the presence of bacterial action which has weakened the protease should be stated. Moreover, it should be stressed that frequently menstrual blood from normal women contains small clots of blood[8] and is incompletely lysed. Further, there is much evidence that the proteases must be considered as "enzyme + inhibitor" systems;[22] it is possible that inhibitors accumulate following lysis of blood depressing further proteolytic activity.

The menstrual fluid resembles prostatic secretion of the dog, and also pancreatic trypsin[13, 15] in many of its proteolytic characteristics. All of these materials dissolve human fibrin; they induce clotting of oxalated rabbit plasma but not the coagulation of purified fibrinogen or prothrombin-free plasma. Canine prostatic fluid differs from menstrual blood in being very active in destroying fibrinogen, an effect which is slight or absent in the menstrual discharge. Trypsin likewise was demonstrable in nearly all of the specimens examined. No differences were observed between a weak solution of trypsin and the menstrual blood.

The results of this investigation lead to the opinion that the menstrual fluid contains liquid blood because it has been previously clotted and the clot has undergone solution. This view is consonant with previous evidence[1, 2, 4, 5, 8] and supports the proteolytic theory of menstrual fluidity.

Conclusions

Fresh human menstrual fluid contains proteases capable of dissolving clots of peripheral blood. This activity is considerably less than occurs in human prostatic fluid or semen; it does not disappear on dialysis and does not destroy plasma fibrinogen. The menstrual fluid does not clot purified fibrinogen but constantly clots oxalated rabbit plasma and occasionally clots human plasma without added calcium ion.

Human menstrual fluid contains small amounts of trypsin as measured by its ability to digest denatured hemoglobin. The proteolytic activity of the menstrual blood is physiologically identical with trypsin.

Rat uterine fluid is more actively fibrinolytic than menstrual blood. This uterine secretion does not digest fibrinogen. The fibrinolytic activity of rabbit uterine fluid is slight. Uterine secretion of the dog does not destroy fibrin; it prolongs the clotting of whole blood, whereas rat secretion and menstrual blood accelerate it slightly.

Acid and alkaline phosphatases values of menstrual blood are moderately increased compared to those values in peripheral blood. The citrate content of menstrual fluid is the same as or slightly higher than peripheral blood.

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Keller, R., and Adrian, J.: Molar Degeneration in Etiology of Early Abortion, Gynéc. et obst. **38**: 332, 1938.

Histologic examination of early ovular remains revealed to R. Keller and J. Adrian (Low Rhine Maternity) the great frequency of molar degeneration. They decided to determine whether such molar changes might not be the cause of many unexplained abortions in the early months of pregnancy. Among 305 curettements for incomplete abortion they found fresh villi in only 96 cases, among which were 21 with molar degeneration. In five cases, all the villi had undergone degeneration, whereas in 16 only part of the villi manifested degenerative changes. Hence 21 specimens among 305 (6.8 per cent) showed molar alterations. This is in striking contrast to the statement usually made that a mole is found only once in 2,000 to 3,000 pregnancies. The authors are convinced that a molar change is responsible for many abortions in the early months of pregnancy. Whereas the diagnosis of molar change may be made with the naked eye in a few cases, histologic study is necessary to prove this point in most cases. Hence all tissue obtained at miscarriages should be examined microscopically as a routine. This procedure is particularly important in view of the possibility that a chorionepithelioma may follow a hydatid mole.

J. P. Greenhill.

HYPOTHYROIDISM AS A PROBLEM IN WOMEN

A Second Report

CARL HENRY DAVIS, M.D., WILMINGTON, DEL.

THE abnormal development of the thyroid gland presents many interesting problems. Until recent years thyroid hypertrophy and toxic goiter received most attention while hypothyroidism was more or less ignored. Following the advice of Marine, in 1917, I began in 1920 to administer iodine in some form to every pregnant woman who showed any evidence of thyroid hypertrophy which, at first, included 41 per cent of my obstetric patients. Further experience convinced me that all women living in goiter areas should have iodine during pregnancy. Prevention of thyroid hypertrophy was the object of this treatment for it was not then appreciated that the iodine might be of importance in aiding the intrauterine development of a more normal thyroid in the infant.

A review of the data included in my 1926 paper entitled "Thyroid Hypertrophy and Pregnancy"[4] indicates that hyperthyroidism was then a more frequent complication than hypothyroidism although three of the 35 patients on whom basal metabolic rate studies were made had rather low rates. I had observed myxedema and knew that it might follow pregnancy. A number of my sterility patients had evidence of hypothyroidism, and a few cretins had been found in Milwaukee, but it was not then suspected that a considerable group of my patients might be hypothyroid cases. In 1927, while developing a program for the section on obstetrics, gynecology, and abdominal surgery of the A. M. A., I requested a paper on the subject of Hypothyroidism in Women from a large clinic, where many thyroid operations were performed each year, and was informed that they had no data for such a paper.

Preparatory to starting a more or less routine determination of the basal metabolic rate in the examination of my office patients, a survey was made of the findings on all females tested in the laboratory at Columbia Hospital, Milwaukee, for a ten-year period ending Dec. 31, 1931. The records of 1,205 women and girls who had been checked on one or more occasions were reviewed. It was found that 410, or 34 per cent, were above plus ten; within the normal limits were 505, or 42 per cent; while 290, or 24 per cent, were below minus 10 per cent. The lower of the two readings made each time was used rather than an average reading. The patients whom I had sent to the laboratory for basal metabolic rate determinations were checked, with the following results: In a total of 172 females tested there were 34 or 19.8

*Presented at a meeting of the Philadelphia Obstetrical Society, January 7, 1943. The first report on this subject appeared in the JOURNAL, October, 1935.

per cent with a basal metabolic rate above plus ten, 91, or 52.9 per cent, within normal limits and 47, or 27.3 per cent, below minus ten. This review convinced me that routine determinations on a considerable number of patients would be justified.

Findings on the first 600 patients tested were published in 1935. My complete Milwaukee series included 763 women and girls and the results are shown in Table I.

TABLE I

Plus 35-40%	1	73 women or 9.6% above plus 10%
Plus 30-35	2	
Plus 25-30	8	
Plus 20-25	10	
Plus 15-20	19	
Plus 10-15	33	
Plus 5-10	56	339 women or 44.4% in normal range
Plus 1-5	69	
0	19	
Minus 1-5	80	
Minus 5-10	115	
Minus 10-15	121	351 women or 46% below minus 10%
Minus 15-20	116	
Minus 20-25	74	
Minus 25-30	32	
Minus 30-35	7	
Minus 35-40	1	

The Milwaukee series furnished basal metabolic rate evidence that a high percentage of the women and girls in that area had varying degrees of hypothyroidism. This series was closed when, in the Autumn of 1936, I moved into a locality where it was believed that most people had normal thyroids. However, in my new location, clinical evidence of abnormal thyroids caused me to begin taking an occasional basal metabolic rate, and after finding a few cases of mild myxedema and several patients with marked hypothyroidism of lesser degree, who had lived in Delaware from birth, I started a new series as a means of determining whether or not there might be a thyroid problem in the Delaware area. Table II records the findings in the first 263 women studied.

A comparison of the Wilmington and the Milwaukee series indicates that so far as can be learned from basal metabolic rate determinations there is as much of a thyroid problem in Delaware as in Milwaukee. Clinical tests with desiccated thyroid in both Milwaukee and Wilmington have indicated that for the most part women with a basal metabolic rate below minus 8 per cent are benefited by the use of small carefully regulated doses of thyroid.

Each series of tests included 126 pregnant women. A comparison of the two groups is possible, from the following:

MILWAUKEE	WILMINGTON
16.7% above plus 10%	5.5% above plus 10%
52.4% in normal range	50.0% in normal range
30.9% below minus 10%	44.5% below minus 10%

TABLE II

Plus 45-55%	1	20 women or 7.6% above plus 10%
Plus 40-45	1	
Plus 30-35	1	
Plus 15-20	5	
Plus 10-15	12	
Plus 5-10	15	120 women or 45.6% in normal range
Plus 1-5	19	
0	10	
Minus 1-5	29	
Minus 5-10	47	
Minus 10-15	55	123 women or 46.8% below minus 10%
Minus 15-20	38	
Minus 20-25	24	
Minus 25-30	5	
Minus 30-35	1	

The tables just presented suggest that hyperthyroidism may be more common in Milwaukee and hypothyroidism in Wilmington. However, my Wilmington group included a number of women with a low basal metabolic rate who consulted me because of abortions or sterility. There is also evidence that hypothyroidism is increasing in America, and it is possible that a series of tests made on pregnant women in Milwaukee today would show a higher percentage of low readings than were noted in my series made prior to 1936.

The basal metabolic rate determinations made for my 1926 paper on women late in pregnancy and just before they left the hospital following delivery, indicated that if a woman had a normal thyroid and took iodine during pregnancy, her rate would remain within normal limits. Since this observation did not agree with the reports of certain other observers a new study has been made in Wilmington on a fairly consecutive group of women who had the first test early in pregnancy, the second late in pregnancy and the third five or more weeks after delivery. A consecutive series was not possible as some women delivered prematurely while others for some reason failed to take the test late in pregnancy. The results of this study are shown in Table III.

TABLE III

		EARLY PREGNANCY		LATE PREGNANCY		POST PARTUM	
Plus	10-15%	1	2%	3	6%	0	
Plus	5-10	2		6		4	
Plus	1-5	3		8		2	
	0	2	56%	0	62%	0	48%
Minus	1-5	5		4		6	
Minus	5-10	16		13		14	
Minus	10-15	10		6		10	
Minus	15-20	6		6		8	
Minus	20-25	6	42%	4	32%	3	52%
Minus	25-30	0		0		3	

This table indicates that a slight increase in the basal metabolic rate may occur during pregnancy but, as in my 1926 report, the present study shows that women who have ample iodine during pregnancy

maintain a fairly stable rate far below that reported by Baer[1] in 1921 and Cornell[2] in 1923. The slight increase in the Wilmington series probably resulted from the administration of thyroid to all women who had a rate below minus 10 per cent and a few of the women in the minus 5 to 10 per cent group who also had thyroid in small doses.

An obstetric tragedy occurred in my practice during the present study. A patient whom I had delivered in Milwaukee three times became pregnant after a lapse of sixteen years and reported to my Wilmington office. Her first basal metabolic rate on June 25, 1941, was plus 18 per cent. Shortly before the onset of labor the rate was plus 32 per cent and her general condition was unsatisfactory. At the time I did not appreciate that she had a definite hyperthyroidism, but twelve hours after delivery she died with a type of cardiac failure observed with toxic goiter. It is possible that large doses of iodine during her labor might have influenced the outcome.

Three other patients with hyperthyroidism have been observed in my Wilmington office. Mrs. I. became toxic following an abortion, and Mrs. W. during the puerperium. Both women responded well to bed rest combined with the administration of iodine and phenobarbital. Mrs. B. whose first test was plus 55 per cent had a history of a thyroidectomy and roentgen-ray treatment of the thyroid. Her response to medical treatment was unsatisfactory and she was referred back to the surgeon who had performed the thyroidectomy.

Myxedema usually can be recognized from a thick dry skin, slow pulse, and subnormal temperature. Overweight is the rule, but Plummer,[6] in 1940, reported that he had found in the examination of 200 cases of spontaneous myxedema 77, or 38.5 per cent, who were below the theoretical normal weight for their height. It has been observed that practically all patients who have a slow pulse and subnormal temperature have a low basal metabolic rate. Barnes,[7] in 1942, reported that in over 1,000 cases in which the basal metabolic rate was subnormal, the body temperature was always subnormal unless an infection was present. This statement in general agrees with my own observations.

Interpretation of the basal metabolic rate may be difficult except in cases where it confirms clinical observations or furnishes a clew to the thyroid as a factor in the development of certain symptoms. A moderate increase of the rate above normal is not definite proof of hyperthyroidism. A decreased rate cannot result from emotional disturbances and it offers more reliable evidence of hypothyroidism, but it must be remembered that this may be a temporary condition secondary to an infection or other cause and that thyroid function may return to normal when the cause of the dysfunction is removed.

My observations during the past twenty years suggest that the thyroid problem in America may be changing, since a considerable portion of the population has received more iodine through the use of iodized salt preparations containing iodine, and in sea food. Only three of the first 35 women tested for me had low basal metabolic rates.

Ten years later 30.9 per cent of the pregnant women seen in my Milwaukee office had low rates, and in my Wilmington series 44.5 per cent were below normal. With the wide use of iodine in the so-called goiter areas, the incidence of thyroid hypertrophy and toxic goiter has materially diminished. In his discussion of Plummer's paper in 1940, Jackson said: "Our group, in Wisconsin, has seen more cases of hypothyroidism in the last five years than in the previous fifteen." It seems reasonable to postulate that a generation of women with abnormal thyroids has passed into a state of hypothyroidism without having the hypertrophy of the thyroid and toxic goiter so frequent a generation ago. While a new generation must grow to maturity before we can determine the effect of iodine therapy on the development of the thyroid during intrauterine life, we do know that it has practically eliminated hypertrophy of the thyroid at birth. Since prescribing iodine for every woman under prenatal care in my office, over 1,500 babies have been delivered with only one that had evidence of an enlarged thyroid at birth. Its mother was a sterility patient who had both iodine and thyroid during pregnancy. The hypertrophy was temporary and disappeared in a few weeks.

Cretinism is no longer a medical curiosity in America. In 1893, Osler was able to collect only 11 cases in the United States, but in 1934, Jackson was able to list 512 cases. New cases are being found each year and some fear that the present high incidence of hypothyroidism may lead to a rapid increase in the number of cretins. This may occur unless we promptly attack the problem through prenatal medication with ample doses of iodine.

DeQuervain is convinced that the harmful changes which may result from improper development of the thyroid are evident by the seventh month of pregnancy, hence the administration of iodine, and, when indicated, thyroid, to the pregnant woman should be started as early in pregnancy as possible. Preferably, the hypothyroid group of women should have treatment for some months before a pregnancy is attempted. For this group, iodine and thyroid medication has been proved to help overcome sterility and to lessen the risk of abortion. There is clinical evidence for believing that when iodine is available for the infant in utero its thyroid may contribute to the thyroxine needs of the mother during the last weeks of pregnancy.

Hypothyroid women have a number of annoying symptoms of which the most common are fatigue, weakness, nervousness, dry skin, falling hair, a tendency to constipation, overweight, menstrual disturbances, sterility, miscarriage, generalized pains, and joint pains. As previously stated, women with dry skin, subnormal temperature and slow pulse are clinically hypothyroid, and the basal metabolic rate will be found low in most cases.

People with abnormal thyroids are found in every part of the United States, and it seems evident that iodine prophylaxis should become

routine in all prenatal care regardless of the place of birth of the patient or her present habitat. Iodine may be administered in different ways, but my preference is for the syrup of hydriodic acid, five drops per day in water being given for a month and then a slightly reduced dose for the rest of the pregnancy. Through adequate medication during the prenatal period, it is believed that it will be possible to prevent thyroid dysfunction from becoming a serious problem in America.

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Discussion

DR. S. LEON ISRAEL.—The magnitude of the thyroid's influence on the physiology of the female generative organs is suggested in the fact that during puberty, a time when it achieves its greatest increment of growth, the average weight of the thyroid gland in females is twice as much as in males. It is difficult, however, to correlate this fact with the varying basal metabolic rates of adolescent girls. There is, moreover, no unanimity of opinion concerning the influence of the menstrual cycle on the basal metabolic rate. The lack of uniformity may result from the fact that the basal metabolic rate is influenced by too many external factors. The usually accepted normal variation of the basal metabolic rate is such that any reading between minus 15 and plus 15 is regarded as being physiologic. Dr. Davis chose in his studies to employ minus 10 and plus 10 as the limits of normalcy. I wondered whether he had made this choice consciously, because he was observing ambulatory patients, in whom the actual metabolic rate is probably 5 per cent lower than that obtained in bed-rested patients.

It would have been most interesting had Dr. Davis been able to compare his patients' rates with changes in their serum cholesterol. Even though the latter is considered a more accurate gauge of hypothyroidism than is the basal metabolic rate, it is difficult to perform repeatedly in office research. It is better to consider the patient with the lowered basal rate as hypothyroid, more especially if she then responds favorably to properly controlled and adequately administered doses of a known potent thyroid preparation.

Dr. Davis makes an important point when he reminds us that the interpretation of the basal metabolic rate may be difficult except where it confirms clinical observation. This is especially true in the treatment of menstrual disorders and sterility, wherein determination of the basal metabolic rate and, as confirmatory evidence, of the level of the blood cholesterol is essential. The typical signs and symptoms of hypothyroidism in terms of classical myxedema are rarely encountered. While it is true that a basal metabolic rate of minus 8 or minus 10 in *normal* women may be ignored, it is also imperative, as Dr. Davis states, to acknowledge that in ambulatory women with either a nonorganic menstrual dysfunction or sterility such slight diminution of the metabolic rate may be of telling value. Therapeutic trial with desiccated thyroid substance is always indicated in such patients. For the same reason, it appears logical to administer the substance to pregnant women having an initially low metabolism.

It is difficult for me to comment on Dr. Davis' thesis of a changing metabolic rate in American women as evidenced by consistently lower rates and a decreasing incidence of thyroid hypertrophy. His own statistics, those of this presentation as well as his widely-quoted earlier ones, attest the usefulness of iodine in maintaining normal metabolic levels in pregnant women. An incidence of only 6 per cent of patients with increased rates late in pregnancy is strikingly low in comparison with most other series, an effect which Dr. Davis attributes to the exhibition of iodine. May I ask, in closing, that Dr. Davis clarify the reason for wishing to control the elevation of the basal metabolic rate of late pregnancy, an increase which seems to stem from the physiologically increased mass of mother and fetus.

DR. DAVIS (closing).—Cholesterol determinations were not made owing to the expense involved. As suggested in my paper, it is my belief that some of the earlier conclusions regarding the increase in the basal metabolic rate during pregnancy are not correct. I made inquiries regarding the Mayo Clinic report and found that the patients did not take any iodine during pregnancy. It is my contention that if a patient with a normal thyroid has adequate iodine during pregnancy her basal metabolic rate will remain within normal limits. The administration of iodine is of major importance for the infant in utero.

I have not been able to confirm the conclusions reached by Dr. Bartholemew in regard to the relation of the thyroid to toxemia.

I summarized the last hundred records of women tested since this paper was written last summer and found that 6 had a basal metabolic rate above plus 10 per cent, 46 were within the normal limits and 48 were below minus 10 per cent. My single plea is for the routine administration of iodine to all pregnant women.

AN ATTEMPT TO CORRELATE THE PRE-ECLAMPTIC STATE WITH A CONGENITAL ANOMALY OF THE KIDNEY*

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(From the Department of Obstetrics, Hahnemann Medical College and Hospital)

MUCH as we pride ourselves on the decrease in the mortality rate in eclampsia, since Stroganoff, the fact remains that there has not been a reduction in the number of cases of pre-eclampsia. The pre-eclamptic state is still with us in spite of the extensive drive in social education resulting in more adequate prenatal care.

One is impressed, first, by the advent of the pre-eclamptic state with the first pregnancy, regardless of age; second, by the frequency with which it recurs in succeeding pregnancies; third, by its characteristic appearance in the last trimester; fourth, by the great number of patients who early have few subjective symptoms, the only objective symptom being hypertension, with few if any urinary findings, and last, by the rapidity with which the blood pressure so often returns to normal six or eight weeks after the termination of the pregnancy. Why?

*Presented at a meeting of the Philadelphia Obstetrical Society, November 5, 1942.

A possible clue was offered by Goldblatt's work[1] on renal ischemia. The similarity between the findings in the experimental animals after moderate clamping of the renal artery and in the early pre-eclamptic state is striking. There was little or no change in the general condition of the experimental animal except for hypertension, little or no impairment in the excretory function of the kidney, no change in blood chemical findings and, finally, complete return to normal with removal of the clamp on the renal artery.

A more recent clue was offered by Campbell[2] and others who observed that men with prostatic hypertrophy and intrarenal kidney pelves had marked hypertension, in comparison with similar patients who had extrarenal kidney pelves. When decompression was slowly carried out in those cases with intrarenal pelves, the blood pressure level returned to normal, and after prostatectomy it remained normal.

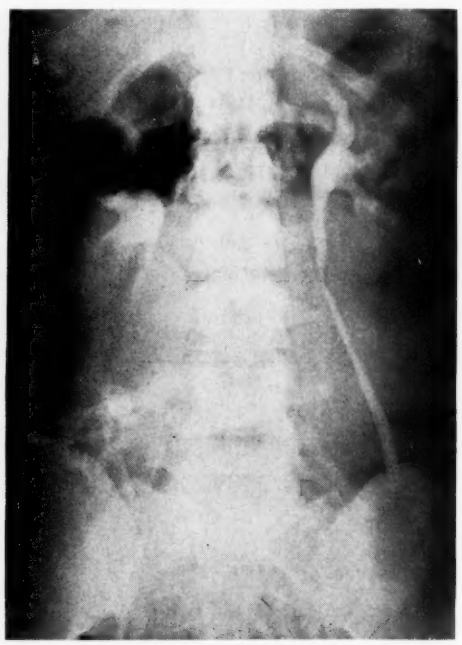

Fig. 1.—Kidney with a typical extrarenal pelvis.

With these clues in mind we attempted to correlate the accepted "arteriolar spasm theory of pre-eclampsia" and the anatomic location of the renal pelvis.

We are all aware of the marked dilatation which occurs in the ureter and renal pelvis during pregnancy, even as early as the tenth week. Whether this is secondary to hormonal action or caused by pressure of the enlarging uterus upon the pelvic ureter is not of importance in this discussion. The facts that there is dilatation of the entire ureter and that the maximum dilatation occurs in the renal pelvis are important in that this dilatation may compress the kidney medulla and thus increase the intrarenal pressure, with resulting tissue ischemia.

We are aware that the capacity of the ureters and renal pelves in the nonpregnant state is 15 c.c., while at term the capacity varies from 32 to 84 c.c. The capacity of the renal pelvis is greater than the combined capacities of the calices; that is, the larger the renal pelvis the smaller the calices, and vice versa.

A kidney pelvis is defined as intrarenal if more than 50 per cent of the pelvis is inside a line drawn from the lateral aspect of one pole of the kidney to the lateral aspect of the other pole on the side of the ureteral attachment.

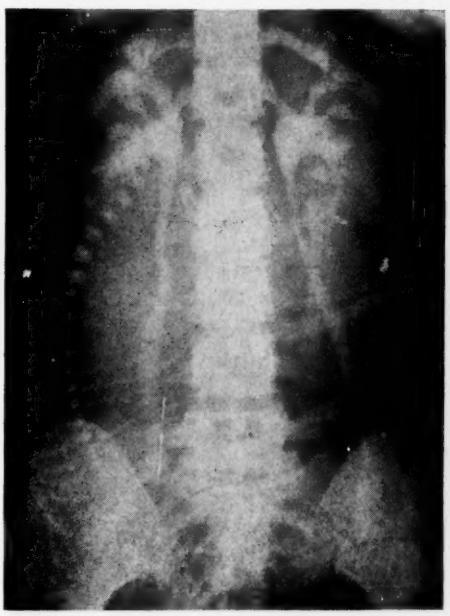

Fig. 2.—Kidney with a typical intrarenal pelvis.

Material and Methods

The material for this report consists of 74 cases, divided into three groups.

1. Twenty-two consecutive patients with pre-eclampsia over a period of six months admitted to the obstetric department of Hahnemann Hospital. The criterion of toxemia was persistence of systolic blood pressure of 140 mm. or more after a forty-eight-hour rest in bed. No case was included in which the blood pressure level was elevated before the fourth month of pregnancy.

2. Twenty-five cases of uropathic conditions complicating pregnancy, on the same service during the same period of time. All cases were nontoxic.

3. A selected group of controls consisting of 27 normal pregnant women near term, who delivered without showing any toxic phenomena.

Routine intravenous urograms were made in all 74 cases. With one exception, all patients were followed to term or termination of pregnancy. The roentgenograms were read by a member of the x-ray department who was intentionally deprived of any knowledge of the clinical status of the patients. He was asked to state whether the kidney pelves were intrarenal or extrarenal. After all roentgenograms were read, the clinical status was correlated with the roentgenologic status. The following results were obtained: Of the 22 toxic cases, 20 patients had intrarenal pelves and 2, extrarenal pelves.

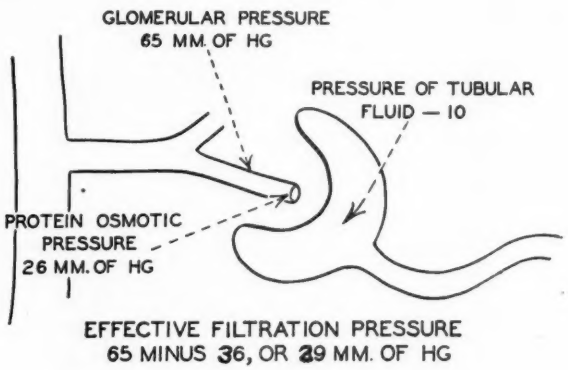

Fig. 3.—Normal glomerular physiology.

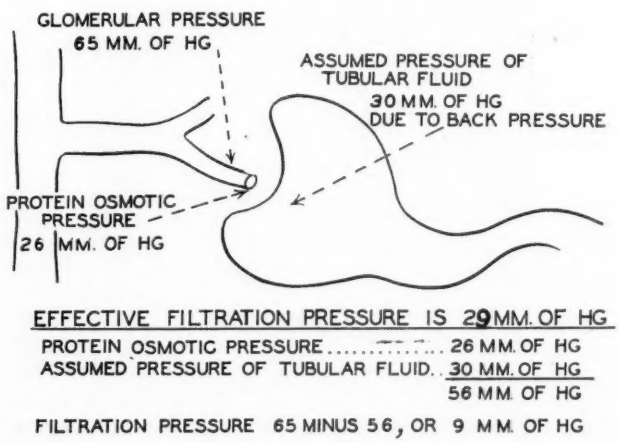

Fig. 4.—Abnormal glomerular physiology.

Of the two with extrarenal pelves one was a patient with a fifth pregnancy at term with a mild toxemia, who in her four previous pregnancies had shown no evidence of the pre-eclamptic state. The other patient was a primipara in whom symptoms of pre-eclampsia developed in the thirty-eighth week. The blood pressure rose to 165 mm. systolic and 80 mm. diastolic, where it persisted for three days and then subsided, and she was delivered at the fortieth week, with a normal blood pressure. Urinary findings were negative.

Of the 25 patients with uropathic conditions complicating pregnancy who did not have toxemia at the time the urograms were taken, 17 had extrarenal pelves, and 8, intrarenal pelves.

All of the 17 patients with extrarenal pelves delivered without showing any elevation in blood pressure or other symptoms of the pre-eclamptic state.

Of the 8 patients who had intrarenal pelves, with normal blood pressure readings, etc., at the time the urograms were taken, one case was lost in the follow-up and in another, a primipara, intra-partum eclampsia developed.

Of the 22 toxic cases, there were 14 primiparas and 8 multiparas. The multiparas were divided as follows:

NUMBER OF PREGNANCIES	CASES
2	1
3	4
4	1
5	2

Of the 8 multiparas in the group with toxemia, there was a history of previous pre-eclampsia in 5. Of the 8 cases, 7 patients had intrarenal pelves and one had an extrarenal pelvis. The one case with extrarenal pelvis was in her fifth pregnancy at term; the patient had no previous history of pre-eclampsia.

In the normal control group, totaling 27 cases, there were 18 with extrarenal pelves and 9 with intrarenal pelves.

Discussion

Can these findings be correlated with our present knowledge of renal physiology?

Goldblatt had produced hypertension by partially clamping the renal arteries in his experimental animals. It makes little difference whether the hypertension was caused by a compensatory rise in blood pressure because of the necessary increase in the rate of blood flow to the ischemic kidney or whether it was the result of a nervous reflex in the ischemic kidney or brought about by the production or storing up of a substance which Goldblatt suggests might be called renin, which acts somehow to cause arteriolar spasm. The fact remains that a decreased flow of blood results in hypertension (Fig. 3).

1. The normal glomerular pressure is 65 mm. of mercury.

2. In the normal kidney the pressure of the tubular fluid is 10 mm. of mercury.

3. All the plasma with the exception of proteins can pass through the permeable membrane of the glomeruli by filtration.

4. A pressure above 26 mm. of mercury is necessary for filtration of the protein elements of the plasma, the so-called colloidal or protein osmotic pressure.

5. Therefore, the filtration pressure may be considered the glomerular pressure minus the total of the colloidal or protein osmotic pressure and the pressure of the tubular fluid; in other words, 65 minus 26, plus 10, or 29, is the effective filtration pressure.

Since normally the kidney pelvis is dilated in pregnancy, we assume that in the presence of an intrarenal kidney pelvis the resulting increased intrarenal pressure must of necessity cause back pressure in the kidney tubule, which in turn must be compensated for by an increase in glomerular pressure or, in other words, an increase in blood pressure.

If the above hypothesis be true, let us assume that something like this occurs (Fig. 4).

Instead of a normal pressure of tubular fluid of 10 mm. of mercury let us assume that the pressure is 30 mm. of mercury, due to back pressure from a distended intrarenal pelvis. The colloidal, or protein, osmotic pressure of 26 mm. of mercury is added to the pressure of tubular fluid of 30 mm. of mercury, the result being 56 mm. of mercury. The filtration pressure is now calculated and found to be 65 minus 56, or 9 mm. of mercury. As previously stated, 29 mm. of mercury is the effective filtration pressure.

Therefore, we theorize that of necessity the vicious circle is broken in only one way, and that is by raising the glomerular pressure, or in other words, the blood pressure.

Conclusion

In a small series of cases, it has been shown that an intrarenal pelvis is more common in the pre-eclamptic state than in normal pregnancy, or even in patients with uropathic conditions complicating pregnancy. An hypothesis is offered to explain these observations. The series is too small to arrive at any definite conclusion. It is necessary to accumulate further data.

Acknowledgments are made to Dr. Edward W. Campbell, for his original suggestion, to Dr. John Scott for his aid in applying the physiology of the kidney to our observation, to Dr. Harry Evans, Sr., of the Department of Roentgenology, and to Dr. Newlin F. Paxson for his advice.

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Discussion

DR. NEWLIN PAXSON.—Dr. Hunter's observations in a small series of cases show that the average ratio of extra- to intrarenal pelvis is approximately 2 to 1 in normal pregnancy, while in toxemic cases the ratio is about 9 to 1 in favor of intrarenal pelves. These observations might be coincidental, but such observations stimulate the imagination. One must ask whether there is an actual back pressure in the ureters? Dr. Hundley, of Baltimore, has shown that in pregnancy there is hypertrophy of the ureters but he did not measure the pressure, but simply created an artificial back pressure to put tension on the ureters to measure rhythmical contractions.

One method of studying this problem would be to take urograms in young married women to see if a prediction of toxemia could be made. All that would be needed would be one intravenous urogram.

FAVORABLE RESPONSE OF ADVANCED ENDOMETRIOSIS TO TESTOSTERONE PROPIONATE THERAPY*

JOHN C. HIRST, M.D., A.B., F.A.C.S., PHILADELPHIA, PA.

THIS report consists of the following: (1) Summary of information from the literature establishing a rational basis for the use of androgens for endometriosis; (2) description of a unique personal case in support of a hyperplasia causative factor of endometriosis; (3) results of hormone therapy in two cases of advanced inoperable disease.

Experimentally, marked progesterone-like effects of androgens have been demonstrated in female rats and rabbits; and ovarian and endometrial atrophy with suppression of menstruation has been produced in monkeys.[1] Rothermich and Foltz[2] showed that androgens reduced urinary gonadotropic hormones in menopausal women.

Following W. O. Wilson's production by prolonged estrogen administration in guinea pigs of subserous fibromyomas resembling human fibroids, Lipschütz[3] not only produced similar uterine and extragenital tumors, but also proved antifibromatogenic and antiestrogenic effects of both testosterone propionate and progesterone. Therefore, since hyperplasia endometrii often accompanies both uterine myomas and endometriosis in women,[4] it would appear from the above that there is definite experimental basis for the use of androgens (and progesterone) in both conditions.

Clinically, there is little in literature concerning the use of androgens for endometriosis, and nothing about progesterone. Greenhill and Freed[1] successfully treated dysmenorrhea, functional uterine bleeding, premenstrual migraine and painful breasts with androgens, but did not include endometriosis. Reports on the use of androgens for fibromyomas give variable results, although except in the case of submucous myomas, excessive bleeding without much effect on the tumors has been reduced.[5] However, we have produced definite involution of the uterus and small fibroids in recent cases.

Aub and others[6, 7] believe that correction of abnormal estrogen overbalance by artificial increase of normally secreted androgen will provide hormone control of certain conditions in women.

Geist and Salmon[8] secured favorable results in over four hundred cases of functional uterine bleeding and dysmenorrhea, premenstrual mastopathies, post-partum breast engorgement, and certain menopausal disturbances (without much masculinizing side effect) using less than 300 mg. of testosterone per month. Their results were attributed to suppression and/or nullification of ovarian estrogens, plus inhibition of endometrial proliferation, of reactivation of uterine musculature, and of hypophyseal gonadotropic activity. These authors also mention the rationale of androgen treatment of *early* endometriosis based on growth-stimulating effect of estrogen (and progesterone), but give no account of its use in actual disease.

*Read at a meeting of the Philadelphia Obstetrical Society, December 3, 1942.

In all reports, effectiveness of synthetic testosterone compounds appeared to be equal whether given intramuscularly as the propionate, orally as methyl tablets, sublingually in propylene glycol, subcutaneously or subfascially in pellets. The last method holds little advantage and some risk of tetanus implantation (Welch[9]). Results were checked not by output control such as the chick-comb method (Frank and others[10]), or the colorimetric titer (Hamblen and others[11]), but therapy was gauged by clinical response, plus endometrial and/or vaginal biopsy.

There is but one reported case of treatment of endometriosis by androsterone.[12] Wilson describes a para i, aged 28 years, pain in rectum and thigh for eight months due to endometrial cystoma of the rectovaginal septum proved by biopsy. Through 4,500 mg. of testosterone propionate injected thoroughout twelve months, this woman's normal menstrual flow was reduced to staining for one to four days every other month, pain was completely relieved, the endometrioma reduced to one-third original

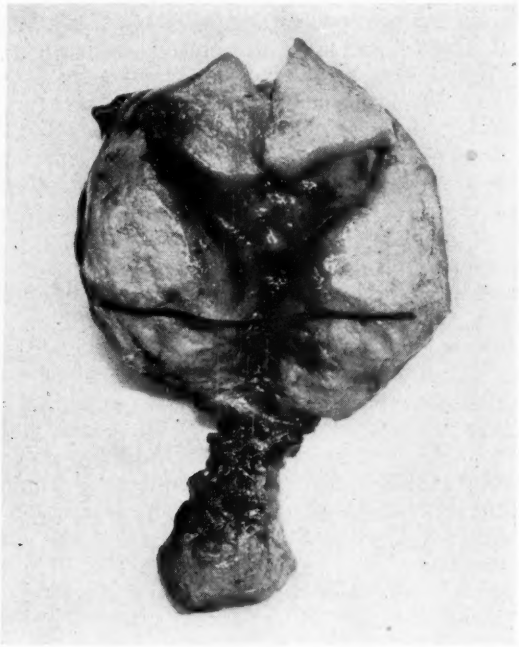

Fig. 1.—Uterus from girl of 19 years, with solid lower uterine segment and cervix, rudimentary blind vagina, secretory endometrium, and fresh corpus luteum at operation. There was no trace of endometriosis in this patient.

size, uterine mucosa atrophied, but cervix, breasts, and vaginal biopsy, as well as libido, were unchanged. However, the voice became husky, habitual hirsutism, and clitoris greatly increased, but secretory endometrium was found five weeks after treatment ceased, and normal menstruation appeared one week later, continuing for six months. Unfortunately, both the pain and endometrial cystoma resumed original proportions.

Certain additional facts suggest a hyperplasia factor in the development of the generally accepted misplaced endometrial cell mechanism (Sampson) of endometriosis. Undoubtedly in addition to myoma uteri,[13]

posterior uterine displacement,[21] surgical implantation,[14] extensive pelvic examinations and tubal insufflations near menstrual times,[15] cervical stenosis, etc., are activating factors. But delayed and infrequent child bearing,[16, 17] as well as proved endometrial hyperplasia in both menstrual and menopausal[18] ages are probable predisposing causes. It is significant that in our large gynecologic ward service of the Philadelphia General Hospital, despite high incidence of myomas, there is relatively little endometriosis, probably due to frequently associated pelvic inflammatory disease. We believe that the high sterility incidence (40 per cent)[19] of endometriosis is a primary dysfunction and not secondary.

In support of hyperplasia as a predisposing cause is one of our private patients, aged 19 years, who presumably for three years had been menstruating painfully into the peritoneal cavity. At operation, there were widely patent tubes, normal ovaries (one with fresh corpus luteum), uterine fundus and endometrium, but a completely solid lower uterine segment and cervix connecting with a rudimentary blind vagina via a thin cord. There was no trace of endometriosis, and this young woman was completely relieved by total hysterectomy with conservation of the ovaries.

Treatment of endometriosis is difficult, since preservation of childbearing and menstrual functions often conflict with radical excisions or irradiation castration, often essential for cure. Although in young women, partial excisions, uterine suspension, cervical dilatation and cauterization, may be helpful, heretofore subsequent radical procedure has been inevitable, especially since presacral sympathectomy is contraindicated (Hurd[20]). Therefore, the treatment and results of two inoperable cases of advanced pelvic endometriosis given below are offered as further evidence of a hyperplasia factor as well as temporary solution of a difficult situation.

Case Reports

CASE 1.—Patient, aged 33 years, married 7 years, birth control 4 years, no conception. Menses 12, 26/4, no pain; basal metabolic rate −19 to −7. Only complaint, sterility. *Diagnosis:* Adherent acutely retroflexed uterus.

Feb. 14, 1939: Operation: Dilatation and curettage, hyperplasia; right chocolate cystectomy (bilateral endometriosis, adherent); right salpingectomy; appendectomy; Coffey uterine suspension. Pathologic report: Tubal endometriosis.

Aug. 6, 1940: Delivered of normal male infant, 7 pounds 13 ounces, by manual rotation, low forceps extraction; good recovery. Sept. 23, 1940: Good postnatal condition.

Oct. 1, 1940, Jan. 22, 1941, and March 7, 1941: Nothing significant. Sept. 3, 1941: Enlarged left ovary.

Feb. 11, 1942: Menstrual history: 21/14/3, scant; basal metabolic rate, ±2 per cent. Small "solid" left ovarian cyst.

March 30, 1942: Rubin test. O.K. Menses: 27-23/short.

June 30, 1942: Left ovarian endometrial cyst *larger,* operation refused. Oreton* 125 mg. per month, intramuscularly, begun.

Sept. 18, 1942: Menses 24/21/4 scant, ovarian cyst behind uterus *larger,* oreton increased (25 mg., q. third day).

Oct. 27, 1942: Menses 24/3½; uterus and left cystic ovary definitely smaller. Treatment continuing as above.

CASE 2.†—*First Admission:* August, 1934, unmarried, aged 23 years; menses, normal; persistent leucorrhea, general abdominal pain, some abdominal rigidity, chief tenderness in right lower quadrant; temperature, 100° F.; white blood count, 13,000.

Operation: Abdomen full of chocolate fluid from ruptured whitish right ovarian cyst, removed with tube and appendix, clinically endometrial, pathologically same (?). Hectic recovery.

Second Admission: July 19, 1939, still single, well until intermittent abdominal pain two weeks, since onset of last period, leading to vomiting all food for last three days; red blood count, 5,500,000; white blood count, 11,500.

Diagnosis: Intestinal obstruction associated with large cyst in left pelvis.

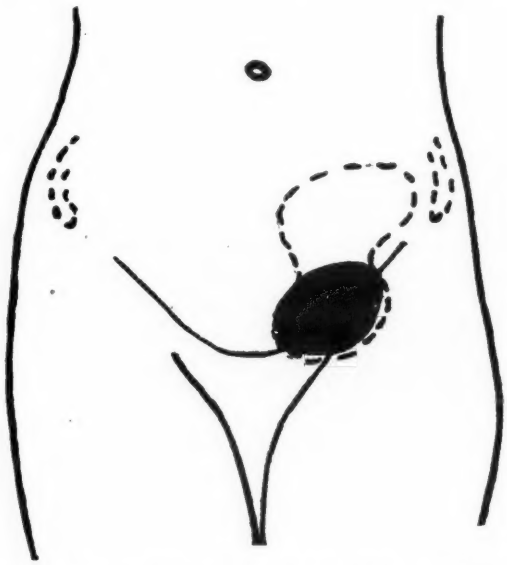

Fig. 2—Reduction of large ovarian endometrioma after treatment by testosterone propionate.

Operation: July 20, 1939, relief of obstruction of ileum adherent to large chocolate cyst of left ovary, which was opened and the pelvis drained (patient refused removal of ovary).

Subsequent History: Married July, 1941; painful menstruation and dysuria, 5 months; pain and obvious swelling in left lower quadrant, due to "dumbbell" shaped tender cystic mass in left pelvis, occupying lower abdomen to 3 f∠⊙ and associated with gaseous distention. Uterus larger than normal, fixed, good position. Weight 112 pounds. Hemoglobin 71 per cent.

*Supplied by the Schering Corporation.

†Through courtesy of Dr. Robert McElroy, from the service of Dr. L. Kraer Ferguson, Philadelphia General Hospital.

Intramuscular injections of Oreton* were given as follows:

May 26 to June 19, 1942, 80 mg. in 10 mg. doses. Felt much better by the fifth injection. Weight 108¾.

June 22 to July 10, 1942, 150 mg. in 25 mg. doses. Pain less severe; menses less, first day.

July 13 to Nov. 23, 1942, 2,050 mg. in 50 mg. doses; 100 mg. per week to Sept. 14, 1942, 150 mg. per week thereafter with the following effects:

July 13, 1942: Breasts smaller; voice husky, occasionally deep.

Aug. 3, 1942: Menstrual flow much less in amount. Left abdominal mass much smaller, so that "clothes fit for first time in a long while, and I feel flatter." Weight 110¼. Libido: same.

Aug. 17, 1942: Feels fine; clitoris (glans and prepuce) much enlarged, one month. Blood pressure 112/60; pulse 62, temperature 97.4° F. Cystic mass about two-fifths original size.

Aug. 30, 1942: Menses five days late, scant, some premenstrual pain.

Sept. 14, 1942: Still aware of small lump in left lower quadrant; voice hoarse.

Oct. 2, 1942: No pain. Menstruated Sept. 27, 1942, one day. Mass same as Aug. 17, 1942. Clitoris still larger. Uterus *small.*

Oct. 27, 1942: Habitual leucorrhea better; same left paraumbilical pulling pain noticeable as after first operation (due to regression of mass?). Some hirsutism, lip, leg, and abdomen (two weeks).

Nov. 23, 1942: No menses since Sept. 28, 1942, but cramps Nov. 21, 1942. Hirsutism increased. Voice deeper and huskier, chiefly with use; weight 113; breasts: distinctly smaller; clitoris still larger; libido less (little); mass same or slightly larger than at last examination (Oct. 2, 1942).

Comment.—Since this patient refused cystoophorectomy or irradiation, androgen hormone therapy was the only available agent, and gave relief of pain and comfort which much more than compensated for secondary effects, so that not one injection was missed in nearly six months of treatment.

We are continuing treatment in tablet form in decreasing dosage to establish minimal requirement by subjective symptoms and objective signs, rather than excretion values; and due to similar antiestrogenic and antifibromatogenic action of both testosterone propionate and progesterone, as well as to known associated endometrial hyperplasia, we plan to substitute progesterone for testosterone, to be reported later.

Conclusions

1. Intramuscular injections of testosterone propionate have a rational basis for the conservative treatment of endometriosis.

2. Large amounts are necessary for the relief of pain and reduction of swelling.

3. Complete absorption of large endometrial masses is not possible in a few months' treatment.

4. This type of treatment is practical for advanced cases where radical excision is contraindicated or refused.

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*Courtesy, Dr. Max Gilbert, Research Division, Schering Corporation.

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COMBINED X-RAY AND EXTERNAL PELVIMETRY*

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(From the Department of Gynecology and Obstetrics, and the Department of Radiology, Boston City Hospital)

WHEN we adopted x-ray pelvimetry at the Boston City Hospital four years ago, we set out to get the most possible information in the simplest manner. We planned to omit all kinds of elaborate apparatus and highly technical details and develop a system of pelvimetry which could be used by any practitioner with the aid of simple x-ray films.

The simplest technique seemed to be the mathematical calculation method originally devised by Ball[1] and modified by Snow.[2] In this method simple anteroposterior and lateral films are taken. The diameters and correction factors are measured directly on the films and the mathematics involved done by the Ball calculator or the slide rule devised by Snow and Lewis.

Material

We used this technique in 200 unselected primiparas, satisfactorily checking our measurements by the Thoms'[3] method and by direct measurements at operation, and the findings were reported in 1940.[4] Since then we have used x-ray pelvimetry in selected cases only, latterly changing our technique somewhat by using it in conjunction with external pelvimetry which we have developed in more detail, especially with regard to the subpubic arch and outlet. We feel, following the dictum of DeLee, that x-ray pelvimetry should supplement and not supplant external pelvimetry and clinical examination of the pelvis.

*Read at a meeting of the New England Gynecological and Obstetrical Society at Boston, December 2, 1942.

The pelvic canal, for all practical purposes, may be divided into 3 planes, the inlet, midpelvis, and outlet, and bony dystocia may be encountered at any one or all of these levels. The study of the bony pelvis involves consideration of contours and measurements. Normal measurements with abnormal contours may cause dystocia just as normal contours with small measurements. Although there is yet no perfect means of measuring the fetal head in utero, we know the variations in its size may vary but slightly despite considerable variations in fetal body weights. If a head departs markedly from the normal this can be diagnosed as a rule by abdominal palpation and the head may be measured

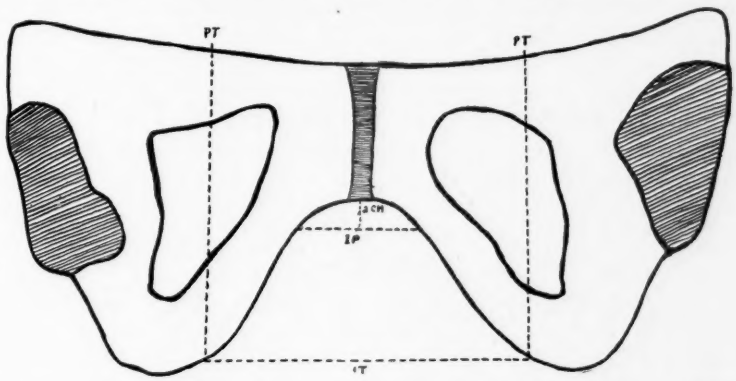

Fig. 1.—Diameters of pelvic outlet: *IP*, interpubic; *IT*, intertuberous; *PT*, pubotuberous.

fairly satisfactorily through the abdominal wall. If the head is engaged or if it is fixed well in the lower uterine segment even before engagement, it may be measured quite accurately by the Ball technique.

Our present method of investigation for cephalopelvic disproportion, preferably done within two weeks of the expected date of confinement, or better at the onset of labor, consists of (1) external pelvimetry, (2) estimation of fetal head size, and (3) x-ray pelvimetry if indicated.

External Pelvimetry

The intercristal, interspinous, external conjugate, and intertrochanteric diameters are measured. If the external conjugate is less than 18.5 cm., we suspect possible narrowing of the conjugate vera. The subpubic arch and outlet are palpated carefully and the following diameters are measured, using the DeLee or Pieri outlet pelvimeters. (The Thoms' outlet pelvimeter cannot be used for the subpubic arch.)

The interpubic diameter is taken on the subpubic arch 2 cm. (about a thumb's breadth) below the lower border of the symphysis and ½ cm. is added to allow for soft tissue thickness (Fig. 1). It is at this plane that the occipital diameter of the fetal head impinges in the process of extension (Fig. 2). Since the occipital diameter of the fetal head usually measures 6 cm., an interpubic diameter less than 6 cm. would require impingement of the occiput lower in the arch with possible dystocia. Since the pubic origin of the levator ani muscles is located in the upper aspect of the arch, a narrow arch would also indicate a narrowing of the fore part of the sling formed by the levators for rotation of the head at midpelvis which might cause dystocia at this level.

The intertuberous diameter is taken between the most medial points of the tuberositis of the ischium and 1 to 2 cm. added for soft tissue thickness. It is at this plane that the biparietal diameter of the fetal head normally emerges, but if it or the arch is small the biparietal diameter may be forced well below it, causing considerable stretching of the perineum with possible severe lacerations unless anticipated by a generous episiotomy. If the intertuberous diameter is less than 9 cm. we measure the posterior sagittal diameter of the outlet, the sum of the intertuberous and posterior sagittal being necessarily 15 cm. or dystocia is suggested and cesarean section probably indicated.

The pubotuberous diameter of Schumann[5] is taken perpendicularly upward from the most medial point of the tuberosity of the ischium to the superior ramus of the pubis and is the measurement of the length of the forepelvis. If this measurement is over 11 cm. we consider the pelvis abnormally long and investigate for a possible funnel-pelvis.

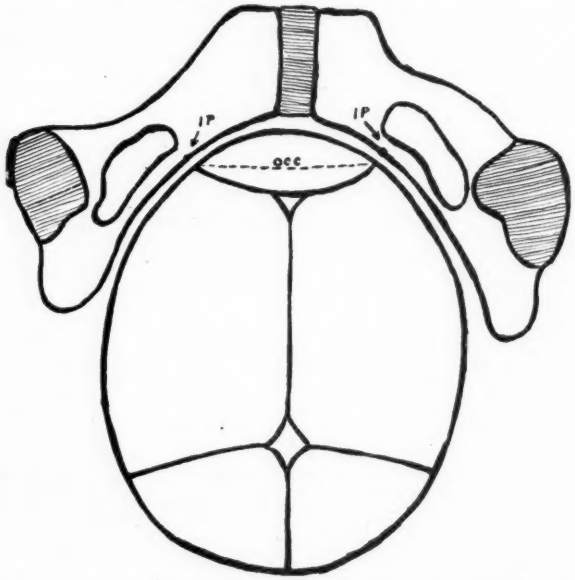

Fig. 2.—Relation of occiput to interpubic diameter: *Occ*, occipital diameter; *IP*, interpubic diameter.

OUTLET (300 CASES)

Interpubic:	6 cm. or over	88%
	Under 6 cm.	12%
Intertuberous:	Over 9 cm.	84%
	9 cm. or under	15%
	Under 8 cm.	1%
Pubotuberous:	11 cm. or under	80%
	Over 11 cm.	20%

The posterior sagittal is taken only if the intertuberous is less than 9 cm. and is measured from the midpoint of the intertuberous diameter to the back of the sacrococcygeal junction, 1 cm. being subtracted to allow for the thickness of the bone.

The patient then lies on her side and the width of the sacrum estimated and the sacrococcygeal junction palpated for any abnormalities. Re-

cently we have added to our study the posterior transverse diameter of the inlet as suggested by Steele and Javert.[6] This is taken from the most medial aspect of the dimples on either side of the rhomboid of Michaelis and helps in differentiating between the gynecoid and android pelves.

Estimation of Fetal Head Size

The usual palpation for determination of engagement of the head is performed. The occipitofrontal diameter of the head is measured directly through the abdominal wall if feasible. Estimation of conformity of the fetal head to the pelvic inlet may be ascertained by using Kerr's technique by which the left index finger in the patient's rectum determines the descent of the head effected by pressure from above the symphysis.

FETAL HEADS (300 CASES)

Occipital:	6 cm. or under	98%
	6.5 cm.-7 cm.	2%
Biparietal:	9.5 cm. or under	94%
	10 cm.-10.5 cm.	6%
Occipitofrontal:	11 cm. or under	84%
	11.5 cm.-12.5 cm.	16%

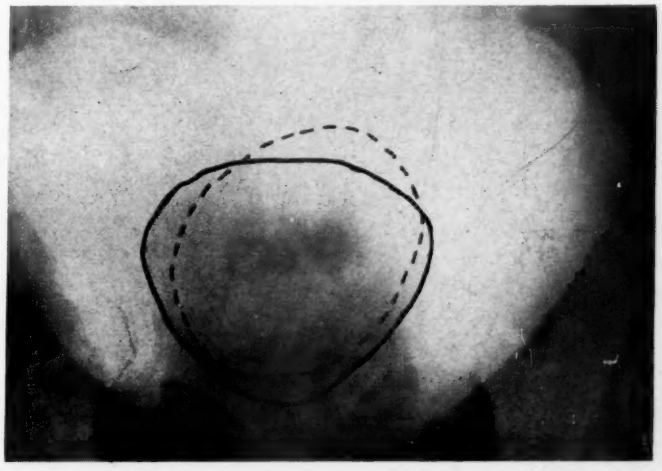

Fig. 3.—A.P. film of inlet with patient in semirecumbent position.

X-Ray Pelvimetry

The following criteria determine the need for x-rays:

1. Primiparas with floating heads at term.
2. Multiparas with a history of previous difficult deliveries.
3. Primiparous breeches with apparently small pelves by external measurements.
4. Cases with narrow subpubic arches and outlets.
5. Elderly primiparas with external conjugates of 18.5 cm. or less.

Since the contour of the pelvic inlet is of paramount importance and since from our experience the most important diameter of the inlet is

the conjugate vera and that of the midpelvis is the posterior sagittal or width of the greater sciatic notch, we have directed our technique to a study of these factors. Thus, we take a film directly through the pelvic inlet with the patient semirecumbent to get a good view of the contour of the inlet (Fig. 3). The inlet is then classified according to the classification of Caldwell and Moloy.[7] A true lateral film is then taken on which we measure the conjugate vera, the anterior sagittal, posterior sagittal, and anteroposterior diameters of the midpelvis, the pubotuberous diameter, and biparietal diameter of the fetal head if possible (Fig. 4). The correction factor for object-table top distance for all these latter measurements which are in the same sagittal plane is one-half the intertrochanteric diameter which we have already taken by external pelvimetry. To this measurement the table top-film distance is added to obtain the object-film distance. The mathematics is completed by the Ball calculator, by the Snow and Lewis slide rule, or by the simple mathematical formula, $O = I\frac{D - d}{D}$ in which O is the object; I the magnified image as measured on the film; D the target-film distance, and d the object-film distance.

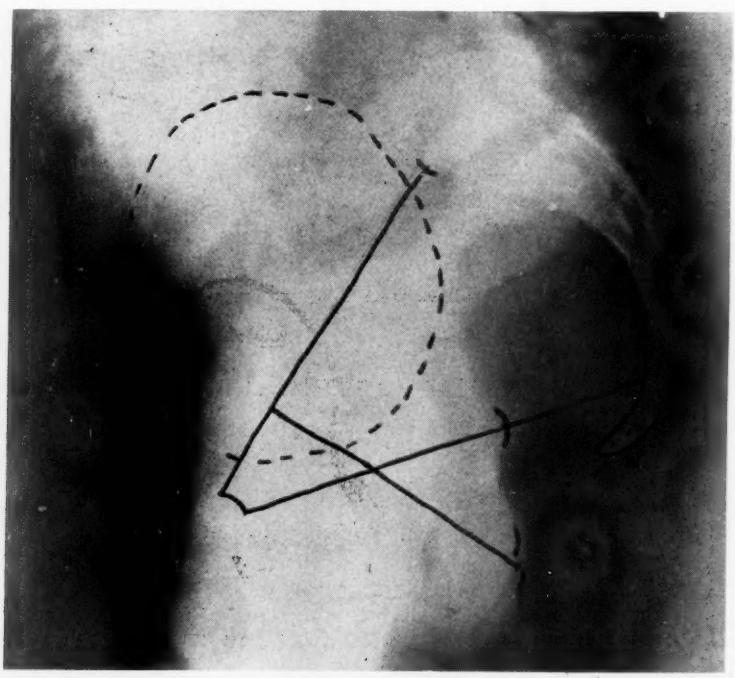

Fig. 4.—Lateral film with lines showing A.P. of inlet, anterior sagittal and posterior sagittal of midpelvis, and pubotuberous, of fore pelvis. Broken line indicates position of head.

Assuming the fetal head to be average in size, the question of probable dystocia at the various planes can be reduced to the following simple observations:

DYSTOCIA AT INLET—MEASUREMENTS

Conjugate vera under 10 cm. in generally contracted pelvis
Conjugate vera under 9.5 cm. in flat pelvis

CONTOUR

Angulation of forepelvis
Flattened posterior pelvis

Since the head enters the pelvic inlet in the majority of cases in an attitude of lateral flexion with the sagittal suture running transversely across the pelvis, the presenting fetal head diameter is the supraparietal-subparietal diameter which normally measures 8 cm. to 8½ cm. thus allowing engagement of the head in even quite narrow anteroposterior diameters. If the forepelvis is acutely angulated, the head is crowded more into the posterior pelvis thus diminishing considerably the available anteroposterior diameter. The flattened posterior pelvis encroaches on the greatest transverse diameter of the inlet necessitating the long axis of the fetal head entering the inlet through a more anterior transverse diameter which may be markedly reduced in size due to the converging walls of the forepelvis.

DYSTOCIA AT MIDPELVIS—MEASUREMENTS

Posterior sagittal under 3.5 cm.
Subpubic arch under 5.5 cm.

CONTOUR

Converging sacrum and pubis
Sacrococcygeal platform

If the head is engaged, we may assume that the patient will deliver from below but we must endeavor to anticipate trouble at the midpelvis and the outlet. If the subpubic arch is narrow we may suspect acuteness anteriorly in the midpelvis with delayed rotation which may also be caused by a narrow posterior sagittal diameter. In these cases x-rays would be indicated to measure the posterior sagittal diameter of the midpelvis and also to note any convergence of the sacrum and pubis and whether the sacrococcygeal junction is angulated in a manner to interfere with descent of the head. If the head is engaged and the arch is normal or large, there is no need for x-rays since the adequate arch would compensate for a narrow interspinous or a narrow posterior sagittal diameter of the midpelvis.

DYSTOCIA AT OUTLET—MEASUREMENTS

Interpubic under 5.5 cm.
Intertuberous under 9.0 cm.
Pubotuberous over 11.0 cm.

CONTOUR

Acute rather than obtuse arch

A narrow arch will necessitate lower descent of the head to find an adequate diameter for impingement of the occiput in the process of extension. This might require a long episiotomy and traction well downward on the pelvic floor before horizontal traction is applied to bring the occiput under the arch. A narrow bituberous also will cause recession of the head necessitating a wide episiotomy. A pubotuberous diameter more than 11 cm. suggests a possible funnel pelvis. If the intertuberous and posterior sagittal diameters combined are less than 15 cm., the possibility of cesarean section must be considered.

Results

The advantages of our methods are best illustrated by the more conservative management of the so-called borderline cases and the decrease in the number of cesarean sections done at the Boston City Hospital for cephalopelvic disproportion.

300 Borderline Cases

Normal	112
Low Forceps	138
Midforceps	20
High Forceps	3
Cesarean Sections	25
Versions	2
	300

The borderline cases were those included in the categories previously mentioned as indications for x-ray pelvimetry. Two hundred and fifty, or 83 per cent, were delivered easily either normally or by low forceps. The 20 midforceps were mostly unrotated posterior heads or midtransverse arrests in which there was no progress after from two to six hours of second stage labor with signs of incipient fetal distress. There were two stillbirths in the midforceps group. There were three high forceps cases which were done because of fetal distress in cases showing an ample pelvis by x-ray and external pelvimetry. These cases were apparently associated with cervical dystocia, and there was one fetal death in the series. There were 25 cesarean sections in the x-rayed group which constituted all but four of the cesarean sections done in the three years, 1939 to 1942, for disproportion. The two internal podalic versions were done for signs of fetal distress with high heads with unruptured membranes and adequate pelves. They resulted in living babies.

In the entire series of 300 cases there were but three fetal deaths and no maternal deaths.

Cesarean Section Statistics

	1937	1938	1939	1940	1941
Deliveries	3,295	3,320	3,262	3,225	3,202
Total cesarean sections	135	142	88	83	91
Primiparas	1,005	1,046	998	915	950
Cesarean sections for dystocia in primiparas	21	31	10	9	10
Incidenc in primiparas	1 in 48	1 in 38	1 in 99	1 in 100	1 in 95

The total number of cesarean sections has decreased markedly since our adoption of x-ray pelvimetry. The incidence of cesarean sections for cephalopelvic disproportion in primiparas has been reduced to one-half the former number without jeopardizing the mother or baby.

The analysis of the 29 cesarean sections done for cephalopelvic disproportion from 1939 to 1942 is as follows:

29 Cesarean Sections—1939-1942

Hours of Labor	Membranes Intact	Morbidity	Membranes Ruptured	Morbidity
No labor	6	0	0	0
Under 12 hours	4	0	5	40%
Over 12 hours	9	22%	5	80%

All but four of the cases were x-rayed. The patients not measured by x-ray were too uncomfortable in labor to be moved to the x-ray department which is considerably removed from the maternity floor.

There were six cases done by election before labor started. These were done in the early part of our work but now all patients regardless of apparent dystocia are usually given some test of labor.

It is evident from the above chart that long labors followed by cesarean section especially if the membranes are ruptured are prone to increase the rate of morbility. Our present policy in borderline cases with membranes intact is to allow twenty-four hours of pains with a frequency of five minutes or under as a test of labor. If the membranes are ruptured, a test of twelve hours is considered adequate. These criteria of course may be influenced considerably by maternal or fetal distress. If there is no apparent cephalopelvic disproportion by external pelvimetry and x-ray, the cause of the dystocia must be sought for in uterine atony or an unyielding cervix and the test of labor broadened accordingly.

All of the cesarean sections in this series were of the low transverse cervical type and there were no deaths.

Summary

1. A system of combined external and x-ray pelvimetry is suggested.

2. This method has reduced the incidence of cesarean section at the Boston City Hospital by 50 per cent with no increase in fetal or maternal mortality.

3. The technique is available to any practitioner and depends largely on clinical examinations.

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THE RELATION OF THE SACRAL PROMONTORY TO THE PELVIC INLET*

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THE anatomist William Turner more than a half century ago wrote, "With the exception of the skull, no portion of the skeleton presents greater individual variations than the pelvis." The truth of this statement has been made greatly manifest in our time, for through the use of roentgen methods has come the opportunity for the study of the bony pelvis on a far greater scale than was possible to our ancestors. The reason for such wide variation in this part of the skeleton must be sought in the fact that the pelvis is developed from a considerable number of bones and that during its growth to the adult state it is subjected to an indefinite number of nutritional, mechanical, and hormonal influences.

The present study is concerned with but one aspect of pelvic variation and that is the pelvic relationships of the upper sacrum, and in particular the position of the promontory of the sacrum in its relation to the plane of the pelvic inlet. In this investigation the roentgenologic findings in 200 primigravid women have been studied. These women were unselected and represent a group who were registered for delivery in the prenatal clinic of the New Haven Hospital during the year 1942.

It is because of the wide variation in position of the sacral promontory in its relation to the bony pelvic canal that some modern investigators have found that for clinical purposes it is necessary to abandon the idea that the superior strait, as described in anatomic texts, should be considered as the plane of the obstetric pelvic inlet. Therefore, from an obstetric point of view the plane of the pelvic inlet is considered to be bounded anteriorly by the upper posterior surface of the pubic symphysis and forward positions of the iliopectineal lines, laterally by the iliopectineal lines and posteriorly by the posterior portions of these lines and the anterior upper surface of the sacrum at the point where the convergence of these lines takes place. The importance of this plane in the mechanism of labor has been emphasized by Caldwell, Moloy and D'Esopo,[1] who state, "We believe that the promontory is too unstable in position to the plane of the inlet to be used as a point of origin of such an important obstetric diameter (the true conjugate diameter). This posterior point should be in the midline of the lower anterior sur-

*This study was made possible through grants from the Clinical Research and Teaching Funds of the Yale University School of Medicine.

face of the first sacral vertebra where the continuation of the iliopectineal lines on either side meet each other.''

That a wide variation exists in the position of the promontory is seen in this study of its relation to the posterior end-point of the antero-posterior diameter of the plane of the pelvic inlet.

In these 200 cases the promontory rested at or near this point in 61 instances,

The promontory rested 1.0 cm. above this point in 30 instances,
The promontory rested 1.5 cm. above this point in 41 instances,
The promontory rested 2.0 cm. above this point in 51 instances,
The promontory rested 2.5 cm. above this point in 12 instances,
The promontory rested 3.0 cm. above this point in 5 instances.

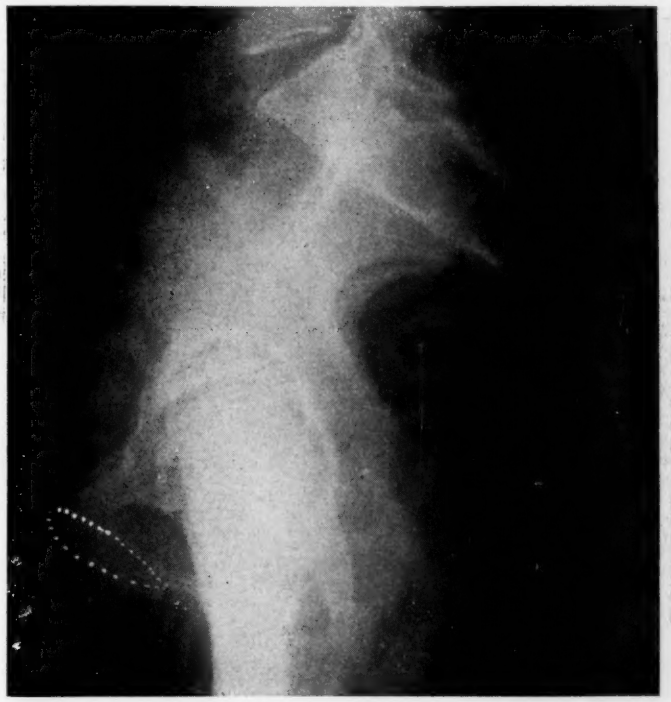

Fig. 1.—Small brachypellic type pelvis, anteroposterior 10.0 transverse 11.5. The promontory rests 2.5 cm. above the posterior end point of the true conjugate. The diagonal conjugate is 12.0 cm. from which it might be assumed that the true conjugate was 10.5 cm., an error which might be costly.

From this evidence it becomes apparent that the position of the forward edge of the sacral promontory is too unreliable to be considered as the posterior end of the true conjugate diameter, for in this series it was at or close to this point in but 30.5 per cent of cases (Fig. 1). It also becomes obvious that because of this positional variation the value of the diagonal conjugate diameter as an index of the true conjugate diameter may be very much questioned. It is generally stated that the true con-

jugate diameter may be estimated from the former by deducting 1.5 to 2.0 cm. according to the height and inclination of the symphysis pubis. Some texts omit the question of height and inclination and simply deduct 1.5 cm. for the true conjugate diameter.

The facts seem to be that the diagonal conjugate cannot be considered a reliable index to the true conjugate diameter and that in some cases information so obtained may be misleading (Fig. 2). In the present series this fact was emphasized by a comparison of Cases 21 and 54, which had identical diagonal conjugate diameters of 13.0 cm. and true conjugates of 11.9 and 10.5, respectively.

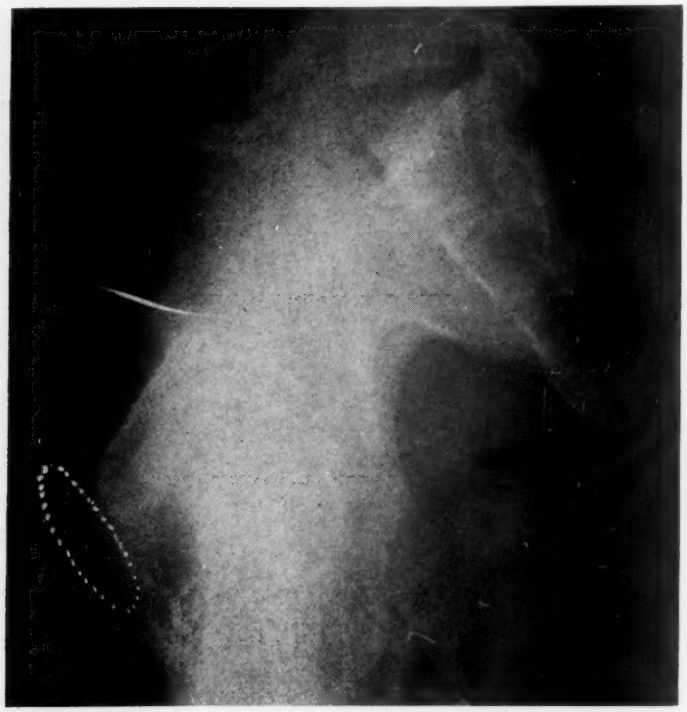

Fig. 2.—Small mesatipellic type pelvis, anteroposterior 10.4, transverse 11.4. The promontory rests 2.0 cm. above the posterior end point of the true conjugate. Roentgenogram shows a breech presentation in a primigravida. The diagonal conjugate is 13.0 cm. from which the true conjugate estimation of 11.5 gives an error of 1.1 cm.

In this series an attempt was made to find out if high positions of the promontory were associated with any particular pelvic grouping according to the division into dolichopellic, mesatipellic, brachypellic and platypellic types. In the series these groups were represented as follows:

Dolichopellic type	30 instances or 15%
Mesatipellic type	84 instances or 42%
Brachypellic type	77 instances or 38.5%
Platypellic type	9 instances or 4.5%

These findings correspond with the findings in 1,100 women previously published,[2] which were for these groups: 18.6 per cent, 45.9 per cent, 32.2 per cent, 3.2 per cent, respectively.

In the 61 pelves in which the promontory was at or less than 1 cm. above the pelvic inlet plane, the division was:

Dolichopellic type	8.2%
Mesatipellic type	37.7%
Brachypellic type	45.9%
Platypellic type	8.2%

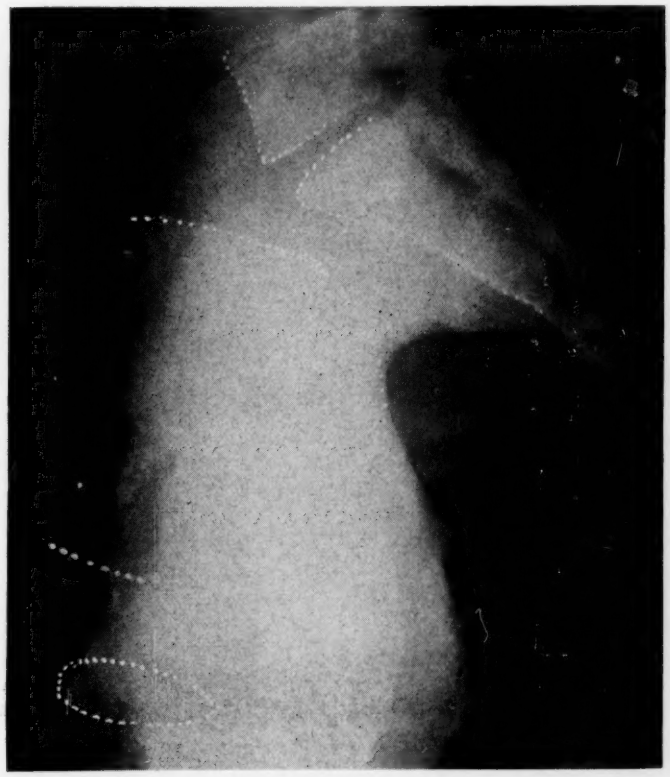

Fig. 3.—The promontory is located near the posterior end point of the true conjugate diameter. In this position it may very definitely influence the descent and position of the fetal head in its engagement in the true pelvis.

In the 71 pelves in which the promontory was 1 cm. or more but less than 2 cm. above the pelvic inlet plane, the division was:

Dolichopellic type	21.1%
Mesatipellic type	38.0%
Brachypellic type	38.0%
Platypellic type	2.8%

In 68 pelves in which the promontory was 2 cm. or more above the pelvic inlet plane, the division was:

Dolichopellic type	14.7%
Mesatipellic type	50.0%
Brachypellic type	32.4%
Platypellic type	2.9%

From this analysis it is apparent that no definite conclusions may be drawn, and that the high promontory position is somewhat, if but slightly, associated with the dolichopellic and mesatipellic types of pelvis.

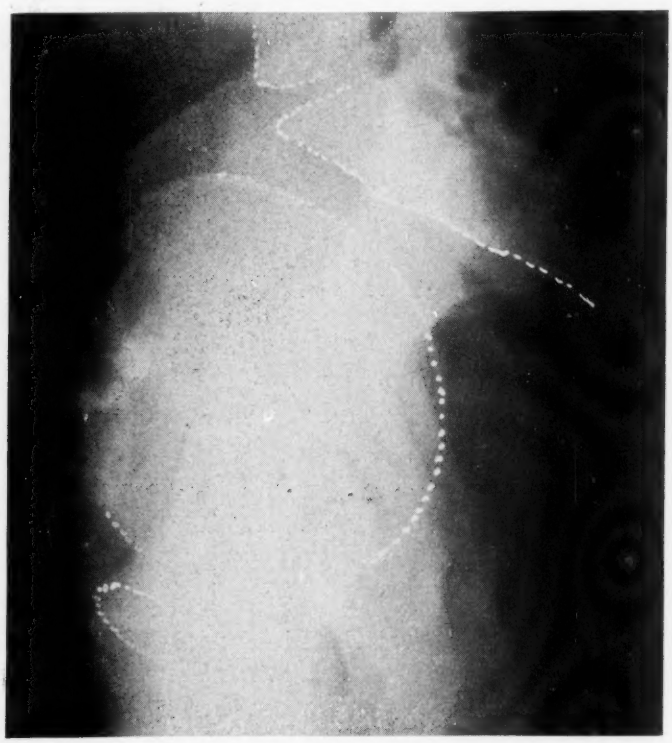

Fig. 4.—The promontory is located 3 cm. above the posterior end point of the true conjugate diameter. Its influence if any in the descent and position of the fetal head in its engagement in the true pelvis would not appear to be important.

In the present series also the reliability of the diagonal conjugate diameter as an index of the true conjugate diameter was determined. For this purpose 1.5 cm. was deducted from the diagonal conjugate and a leeway of 0.25 cm. + or − was allowed for the true conjugate. The result showed that the diagonal conjugate could be used as a satisfactory criterion in 76 instances, or but 38 per cent of cases.

Because of the variation in the position of the sacral promontory, it is apparent that the usual concept of the role played by this protuberance in the pelvic engagement of the fetus and in the mechanism of labor must be somewhat modified. Except in those instances where the promontory is at or near the posterior limits of the plane of the pelvic inlet it is difficult to see how in high positions it can play a very major part in the mechanism by which the fetal head settles into the pelvis. The fact is seen to advantage in Figs. 3 and 4. However, it should not be forgotten that in certain instances (probably rarely) even when the promontory occupies a somewhat high position it may project forward and the distance from the upper posterior symphysis to the promontory be less than that of the true conjugate diameter (Fig. 5).

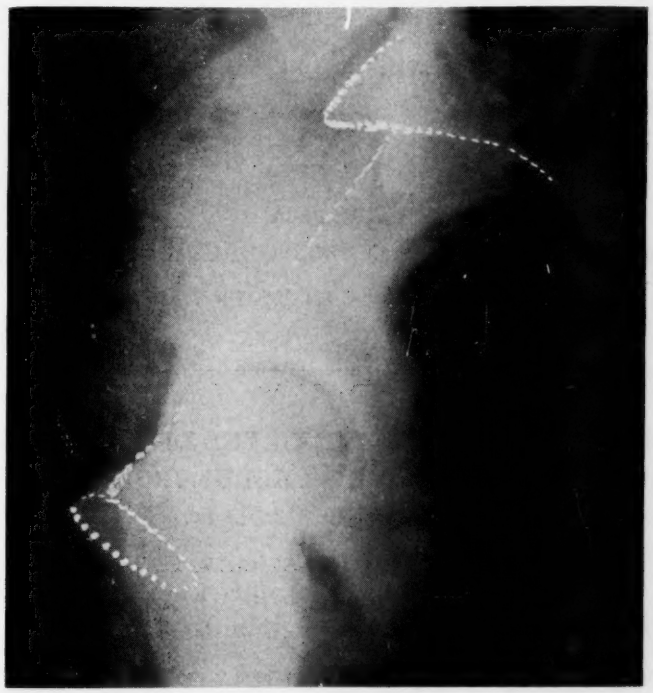

Fig. 5.—Rarely when the promontory is located above the posterior end point of the true conjugate a forward position exists which makes the symphysis-promontory distance less than the true conjugate, in this instance 11.5 and 11.2 cm., respectively.

A question arises as to whether high positions of the sacral promontory are definitely associated with the so-called assimilation pelvis. There did not seem to be any direct evidence of this in the series, but it should be stated that the diagnosis of this type of pelvis from the single lateral roentgenogram cannot readily be made because all of the segments of the lumbar spine are not visible and in many instances the segmentational differences in the lower sacrum and coccyx are not easily distinguishable.

In conclusion, it may be stated that because of the variation in position of the sacral promontory the estimation of the true conjugate diameter based upon the length of the diagonal conjugate diameter is subject to error and pelvic capacity so determined should not be expressed in exact terms. In the present series the estimation of the true conjugate diameter based on the length of the diagonal conjugate was only approximately correct in 38 per cent of cases. Because of the variation in position of the sacral promontory the part played by this protuberance in the engagement of the fetal head may be either important or unimportant.

This study emphasizes again that roentgenologic methods are an important adjunct to the usual diagnostic obstetric procedures, for with the added knowledge that they furnish many of the mechanical problems of labor will be better understood and operative interference made a more intelligent procedure. In our own clinic the experience obtained by the routine use of roentgen pelvimetry in 2,000 primigravid women delivered during the past seven years confirms this opinion with increasing strength.

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THE EFFECT OF COMPLEMENTING THE DIET IN PREGNANCY WITH CALCIUM, PHOSPHORUS, IRON, AND VITAMINS A AND D*

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THERE have been a number of reports concerning the calcium, phosphorus, iron, nitrogen, and vitamin D requirements of the pregnant woman, but the actual number of patients studied is comparatively small. A series of metabolic studies were made by us as a part of an investigation of the therapeutic value of added amounts of calcium, phosphorus, iron, and vitamins A and D.

The patients were divided into four groups:

(1) Control.
(2) These patients received a proprietary cereal for its calcium, phosphorus, and iron content.

*Read at a meeting of the Chicago Gynecological Society, January 15, 1943.

This study was supported in part by a grant from Mead Johnson and Company, who also supplied the special cereal and vitamins.

(3) These patients were given 39,900 international units of vitamin A and 5,550 international units of vitamin D daily.
(4) These patients were given both the cereal and the vitamins.

Patients in the special groups were on the same medication throughout pregnancy. The average amount of the special cereal taken daily ranged from 30 to 50 Gm., but in the hospital the patients ingested approximately 100 Gm. (One hundred grams contained 0.78 Gm. calcium, 0.62 Gm. phosphorus, and 30 mg. of iron.)

The patients were hospitalized for a period of at least seven days and the diet and collection of excreta were continued throughout the hospital period. Balance studies were made over a five-day period, beginning thirty-six hours after admission. Our regular house diet was used in all cases, with oatmeal as the standard cereal, except in those patients receiving the special cereal, it was substituted for the oatmeal.

The data pertinent to each patient are summarized in Table I. Eleven of the 14 patients were primiparas because they, having no children, could be persuaded to spend the necessary periods in the hospital. The weight gain occurred during the period of observation, which is given in Table I. Eight patients gained excessively but only two developed toxemia. One pregnancy terminated in a premature delivery of a stillborn fetus. There was nothing striking about the birth weights of the babies. All of the patients had breast milk but almost all had to use complementary feeding.

TABLE I. DATA CONCERNING THE SUBJECTS

NO.	AGE	GRAVIDA*	PARITY*	HEIGHT CM.	MINIMUM WEIGHT KG.	MINIMUM SURFACE AREA	WEIGHT GAIN KG.	WEIGHT BABY	NO. WEEKS AT DELIVERY	COMMENTS
1	18	i		151	32.5	1.24	17.0	2815	40	
2	18	ii	i	161	50.5	1.51	9.3	3165	40	
3	16	i		159	62.3	1.63				
4	21	i		151	58.6	1.53	16.9	3640	43	Toxemia
5	25	i		162	46.4	1.47	10.5	2945	38	
6	27	ii	i	158	67.0	1.67				
7	19	i		155	53.1	1.50	14.4	3610	40	
8	19	ii		162	49.4	1.50	13.8	3330	42	
9	22	i		155	51.5	1.48	10.9	3405	40	
10	20	i		158	57.5	1.58	14.1	2315	32	Toxemia Stillbirth
11	25	i		154	46.5	1.41	12.2	3300	39	
12	41	v	iii	153	60.2	1.56	6.4	3075	37	
13	24	i		163	57.4	1.60	16.3	3525	41	Postpartum hemorrhage; transfusion
14	18	i		159	56.5	1.57	13.5	4675	43	

*Gravida, number of pregnancies; parity, number of viable babies.

The intake for the various substances studied as well as the balances are given in Table II.

The calcium and phosphorus balances were positive in all 25 antepartum periods. There were 8 post-partum periods. Only one patient had a negative balance. If the calcium and phosphorus secreted in the milk had been included, all balances after delivery would have been negative.

TABLE II. AVERAGE DAILY INTAKE AND BALANCE*

NO.	GESTATION OR PUERPERIUM WEEKS	WEIGHT KG.	CALCIUM (GM.)		PHOSPHORUS (GM.)		NITROGEN (GM.)		IRON (MG.)	
			INTAKE	BAL.	INTAKE	BAL.	INTAKE	BAL.	INTAKE	BAL.
					Group I					
1	15	32.5	1.330	0.625	1.525	0.525	11.23	2.85	14.84	8.77
	28	43.6	1.440	0.448	1.683	0.57[illegible]	12.21	2.22	16.24	3.62
	38	49.0	1.434	0.336	1.673	0.633	12.13	2.44	16.15	7.33
	2 pp.	37.4	1.418	0.695	1.596	0.291	11.94	1.43	15.83	11.35
	6 pp.	41.0	1.409	0.495	1.545	0.55[illegible]	11.73	3.20	13.57	5.56
2	25	54.6	0.702	0.148	0.932	-0.008	7.34	-2.37	13.39	4.89
	39	59.8	0.819	0.564	1.035	0.095	7.79	-1.16	11.46	5.46
3	19	62.0	1.441	0.331	1.751	0.861	12.61	3.11	17.47	10.37
					Group II					
4	24	58.6	1.462	0.592	1.612	0.332	11.36	0.69	22.54	9.61
	34	67.0	1.637	0.497	1.726	0.436	11.87	1.10	24.21	15.53
	39	73.0	1.436	0.410	1.668	0.468	12.10	-1.64	16.02	-28.17
	2 pp.	62.0	1.229	0.826	1.458	0.248	10.66	0.87	13.75	9.99
	6 pp.	60.3	1.389	0.618	1.615	0.555	11.78	2.80	15.66	10.21
5	28	52.8	1.488	0.821	1.614	0.45[illegible]	11.39	2.38	21.91	12.16
	2 pp.	46.6	1.543	0.539	1.668	0.358	11.50	1.54	21.76	12.15
6	26	67.0	1.481	0.811	1.615	0.735	11.47	2.83	20.96	10.06
					Group III					
7	20	57.0	1.438	0.508	1.682	0.272	12.18	1.86	16.18	8.51
	30	63.7	1.412	0.402	1.649	0.309	11.92	0.79	15.95	9.43
	2 pp.	61.6	1.240	0.456	1.372	-0.458	9.79	-1.91	13.14	7.42
8	39	61.3	1.318	0.818	1.610	0.790	11.79	2.74	16.15	10.86
9	15	55.0	1.160	0.476	1.481	0.431	11.02	1.19	15.84	6.40
	30	61.5	1.440	0.430	1.684	0.524	12.18	3.88	16.24	7.57
	2 pp.	52.7	1.440	0.174	1.683	-0.797	12.21	-1.38	16.24	5.69
					Group IV					
10	17	60.0	1.424	0.673	1.672	0.552	12.13	2.36	16.32	6.41
	30	71.6	1.442	0.621	1.685	0.725	12.19	0.92	16.28	6.92
11	16	47.2	1.628	0.331	1.733	0.403	12.07	0.43	23.63	4.75
	33	54.5	1.648	1.021	1.748	0.868	12.14	2.75	24.02	13.97
12	23	66.0	1.653	0.321	1.752	0.47[illegible]	12.14	2.06[illegible]	24.10	8.17
	38	62.0	1.454	0.171	1.466	-0.294	9.14	-1.85	20.39	-16.29
13	25	65.5	1.581	0.436	1.696	0.876	11.86	2.07	22.92	12.72
	40	73.8	1.410	1.068	1.558	0.896	11.10	3.59	19.37	12.37
14	18	58.0	1.657	-0.903	1.757	0.428	12.18	0.434	24.18	5.09

*The negative balances are indicated by a minus sign.

The articles published by Macy and Hunscher, and especially the extensive bulletin published by Coons and co-workers, summarize all data on metabolism in pregnancy published prior to 1935. These studies

indicated that an average intake of 1.320 Gm. of calcium resulted in a retention of 0.194 Gm. per day during the last three months of pregnancy. Likewise, an average daily intake of 1.713 Gm. of phosphorus resulted in a retention of 0.289 during the last three months of pregnancy. Our balances are, on the whole, in agreement with the ones previously reported. Individually and collectively, we can see no change in the metabolism of calcium or phosphorus in those patients who received added calcium or vitamins A and D. Our patients generally had slightly larger positive balances than the average figures reported by Coons.

Approximately one-half of the nitrogen balances compiled by Hunscher and associates indicated a retention of nitrogen of from 1 to 3 Gm. daily, with an average of 2.28 Gm. nitrogen. The retention per kilogram of body weight varied from 0.14 to 0.19 Gm. The average intake of 13.70 Gm. of nitrogen, based on Landsberg and Coons' data, indicated an average retention of 1.96 Gm. A nitrogen intake below 10 Gm. per day usually resulted in a negative balance.

Our data for the nitrogen metabolism are given in Table II. Only two patients had a negative balance during pregnancy.

Hunscher and co-workers found from their work and a survey of the literature that the maternal body retains a considerable excess of nitrogen during pregnancy beyond that required for the fetus and its adnexa. Following parturition there is a loss which persists over the first two weeks or more of the puerperium.

An interesting observation was made by Melnick and Cowgill, who found that when pregnant dogs were fed on protein-free diets at a high level of caloric intake and were subjected to their standardized plasmapheresis technique, it was possible to deplete the animal of its reserve serum protein and to reduce the serum protein concentration to the basal level (3.5 to 4.2 per cent necessary for the formation of edema) within less time than normal. Once the basal serum protein level is attained, the pregnant or lactating dog exhibits a marked impairment in its ability to regenerate serum protein. This inability to form serum protein may be due to the needs of the fetus or to faulty absorption by the mother.

There is an increased need for iron in pregnancy to take care of the increased blood volume and for the fetal demands for its own body development and also as a reserve for postnatal growth. The iron content of the newborn infant ranges from 0.266 to 0.937 Gm. The average daily transfer of iron from mother to fetus during the first two-thirds of pregnancy has been estimated to be 0.4 mg., and during the last third to be 4.7 mg. daily.

In one series, Coons and co-workers report an average intake of 14.72 mg., and a storage of 3.16. In another series, the intake ranged from 9.45 to 34.88, with an average of 15.74, and an average storage of 2.45 mg., with a range of from 0.23 to 6.88 mg. of iron daily. There were no

negative balances, but approximately 75 per cent of the studies were below that of the estimated fetal demand. They felt that the low retentions were not due to a low total iron intake, but probably to a deficiency or other dietary factors which promote the utilization of iron.

Coons also found that on comparable levels of iron intake in the usual diet, the retention by a group of southern women averaged almost 50 per cent lower than that for some Chicago women during corresponding periods of pregnancy. Coons also mentions that the quality, as well as the quantity, of iron intake, physiologic demands of pregnancy, and slight digestive upsets in pregnancy seem to be important factors in iron retention.

Toverud determined the iron balance in ten women in the last trimester of pregnancy. The daily intake varied from 7 to 28 mg. Two patients had a positive balance on an intake of 13 mg., and two had a negative balance on an intake of 15 mg.

Our data are given in Table II. Most of our patients showed a positive balance with an intake of iron ranging from 12 to 24 mg., with an average of 18.8 mg.; the retention ranged from a negative to a positive balance of 12.57 mg., with an average of 8.54 mg. One patient had a negative balance of 28.17 mg., with an intake of 16 mg.

We have listed in Table III the minimum, maximum, and average intake and balances per kilogram of body weight. The figures for the intake per kilogram for each subject tend to be more constant than the figures for the daily intake per subject. Since the weights are changing, this is of importance. Furthermore, the daily balances per kilogram indicate that although some patients are in positive balance, yet the amount retained per kilogram of body weight is far less than the average.

TABLE III. DAILY INTAKE AND BALANCE IN MG. PER KILO BODY WEIGHT DURING PREGNANCY

	CALCIUM			PHOSPHORUS			NITROGEN			IRON		
	MIN.	MAX.	AV.	MIN.	MAX.	AV.	MIN.	MAX.	AV.	MIN.	MAX.	AV.
Intake	12.9	40.9	24.8	17.3	46.9	28.3	150.4	345.6	195.0	0.19	0.50	0.32
Retention	2.7	20.3	10.0	1.6	16.2	9.0	7.49	87.8	34.8	0.09	0.39	0.16

The numbers of patients in each group are too small for comparative purposes. However, other data were studied in groups containing 95 to 176 patients. Differences were present but either they were not significant or if significant the number of patients was too small.

Summary

Metabolic studies of calcium, phosphorus, nitrogen, and iron were made on 14 patients at intervals during pregnancy. Although the patients were given different diets, no significant changes were noted. The intake and retention of the substances studied were essentially similar to those reported in the literature.

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THREE CASES OF SULFATHIAZOLE TOXICITY IN OVER NINE HUNDRED WOMEN TREATED FOR CHRONIC GONORRHEA

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NINE hundred and four female patients with gonorrhea alone or with gonorrhea combined with syphilis were admitted to the venereal service of the Kingston Avenue Hospital during a period of eighteen months. All of these were admitted with positive gonorrheal cultures and of these, many had positive spreads. They were hospitalized for periods varying from two to four weeks at the request of the Health Department in order to control the spread of venereal disease.

Careful histories, physical examinations, and laboratory tests which included blood counts, sedimentation rates, and urinalyses were routine. The patients received dosages of sulfathiazole varying from 3 to 4 Gm. daily for from seven to ten days. Albuminuria, hematuria, anemia, and leucopenia were contraindications to the administration of the drug. Urine examinations and blood counts were done periodically during treatment. Our previous experience had taught us that blood levels of sulfathiazole were of slight significance, and we abandoned them except in toxic cases.

Marked toxic symptoms were noted in only three cases* in the entire group. Minor toxic symptoms (i.e., dizziness, slight nausea, headache, faintness, and mild and transient rashes) were present at times. The patients were confined to bed only if symptoms appeared.

The following three severe toxic cases were encountered:

CASE 1.—Miss J. A., white, aged 30 years, was admitted to the Kingston Avenue Hospital on July 11, 1942, because of a positive gonococcal culture and a four-plus Wassermann. At the age of thirteen she became aware that she had congenital syphilis and was treated occasionally with arsenic and bismuth. She had an appendectomy at fourteen years of age. At twenty-two, she was stabbed in the abdomen necessitating resection of two inches of intestine and was discharged after two weeks. Three years prior to admission the patient was at home six weeks with "a pelvic inflammation." Her menstrual history was negative. She denied pregnancies.

*Two of these cases need never have occurred had the patients disclosed pertinent details of their past histories. See conclusions.

Physical examination revealed Hutchinson's teeth, and two lower abdominal scars. Vaginal examination disclosed negative urethra, Skene, and Bartholin glands. The cervix was not eroded, but showed a moderate purulent discharge. The uterus was small, anterior, and mobile. Both tubes were thickened.

The urine examination was negative, blood count 72 per cent hemoglobin; 8,100 white blood cells; 55 per cent polymorphonuclears and 45 per cent lymphocytes. Sedimentation rate was 18 mm. in forty-five minutes.

She received 4 Gm. of sulfathiazole daily for five days. On the sixth day she had a flare-up of the adnexa inflammation with severe abdominal cramps. Examination revealed tenderness in both lower quadrants. The vaginal examination was negative except for tenderness in the fornices. The next day, abdominal pain continued and there was tenderness over both lower quadrants and over the kidney areas. She vomited sixteen ounces in the morning and twenty ounces in the afternoon. Between 7 A.M. and 9 A.M. she passed only 5 c.c. of urine and upon catheterization only 2 c.c. of bloody urine were obtained. The temperature was 99° F., pulse 84, blood pressure 120/80. The blood count was 4,000,000 red blood cells; hemoglobin 70 per cent; 9,000 white blood cells and polymorphonuclears 65 per cent. In the evening the temperature rose to 100° F., pulse 100, and respiration 20. The urine showed two-plus albumin, many red and white blood cells, and occasional sulfathiazole crystals. At 11 A.M., she received 500 c.c. of 10 per cent glucose in saline intravenously, and at 4 P.M. another 500 c.c. of 5 per cent glucose. At 4 P.M. she voided 5 c.c. of urine and upon catheterization an additional 2 c.c. was obtained. That evening 10 c.c. of urine was obtained by catheter. The next day, July 16, she passed 2 c.c. of urine and another ounce upon catheterization. Later in the day, she vomited 6 ounces of greenish fluid and voided 7 ounces of urine. Ureteral catheterization showed no block in either kidney and no crystals were obtained. The blood findings were 4,000,000 red blood cells, 72 per cent hemoglobin, 21,000 white blood cells, 79 per cent polymorphonuclears, and a trace of sulfathiazole in the blood. The blood chemistry showed nonprotein nitrogen 29 mg. per cent and blood sugar 98. The blood pressure was 140/95, temperature 102° F., and the pulse 96. The urine examination revealed two-plus albumin, many white and red blood cells. 700 c.c. of 10 per cent glucose were given intravenously twice daily. On July 17, the physical examination revealed tenderness over both lower quadrants and over both kidney regions, but much less than on the previous examination. The vaginal examination disclosed the left adnexa tender and about 8 cm. in diameter, and the right adnexa thickened and tender. She passed 4 ounces of urine which showed one-plus albumin and fewer white and red blood cells than previously. The patient went home on a release the next day.

Two days after the onset of toxicity we obtained the following additional history which no doubt would have contraindicated the administration of sulfathiazole. A sister told us the patient was a heavy drinker and imbibed about two quarts of liquor daily. She also informed us that the patient attempted suicide with bichloride of mercury about four years prior to admission. Upon obtaining this additional information, a diagnosis of nephrosis was made since ureteral catheterization showed no blockage with sulfathiazole crystals.

CASE 2.—Mrs. M. C., white, aged 29 years, was admitted to the Kingston Avenue Hospital on July 6, 1942, with a positive gonorrheal cul-

ture from the urethra and cervix. This case is particularly interesting because of the pathology to the liver which is very often affected by sulfa drugs. At the age of seventeen, she had a spinal fixation with a tibial graft for a bone tuberculous process. She denied pulmonary tuberculosis. The menses were normal. She suffered with a "bladder condition" prior to admission. She had one child five years ago which died a few hours after birth.

Physical examination revealed signs of tuberculosis in the left upper lobe, a scar over the lumbar vertebrae, and also over the left tibia. Pelvic examination showed a purulent discharge from the urethra, Skene's glands, and the cervix which was lacerated. The uterus was small, anteverted and pulled to the left by the enlarged adnexa.

X-ray showed a productive tuberculosis in the upper lobe of the left lung. Urine examination was negative. The blood findings were 74 per cent hemoglobin, 4,600 white blood cells, 60 per cent polymorphonuclears, and 40 per cent lymphocytes.

After receiving 4 Gm. of sulfathiazole daily for seven days, the patient complained of nausea and weakness. Three days later the patient developed jaundice and complained of weakness. The next day the icterus increased. The icteric index was 55. The van den Bergh test was positive direct, immediate. The blood chemistry showed nonprotein nitrogen 27, and sugar 75. The blood count was 4,000,000 red blood cells, 82 per cent hemoglobin, 6,600 white blood cells, and 68 per cent polymorphonuclears. The sedimentation rate was 18 mm. in thirteen minutes. No sulfathiazole was found in the blood or urine. The urine was positive for bile and urobilinogen. The stools were clay colored.

The patient was given 50 c.c. of 50 per cent glucose intravenously; twice daily; 1 c.c. of vitamin "B" complex daily; a high carbohydrate and protein, and a low fat diet. Her condition remained unchanged for ten days when nausea diminished and jaundice lessened. The duodenal contents showed a trace of bile before and after magnesium sulfate. The blood chemistry revealed 142 mg. per cent of total cholesterol. The fragility test for red blood cells started at 0.40 per cent and was not complete at 0.28 per cent. Bile and urobilinogen were present in the urine. On July 30 the icteric index was 35 and stools were normal. On August 4 the jaundice was very mild, her general condition was improved and upon signing her release she was discharged.

A review of the facts in this case emphasizes the necessity for a thorough investigation of the past history. This patient had a toxemia of pregnancy with eclamptic seizures.

CASE 3.—Miss E. H., Negress, aged 21 years, was admitted to the Kingston Avenue Hospital on May 12, 1942, with a positive gonorrheal culture from the cervix and urethra.

The past history and physical examination were negative. Except for a purulent discharge from the cervix and urethra the pelvis was negative. The laboratory findings were: 3,600,000 red blood cells, 68 per cent hemoglobin, and 8,400 white blood cells. The urine was negative. The sedimentation rate was 18 mm. in thirty-five minutes.

On May 14, she was given 1 Gm. of sulfathiazole four times a day. Four days later she complained of pains in the lower abdomen and legs. The temperature was 102.2° F., pulse 114, and respiration 24. The lower abdomen was tender, but there was no rigidity. Pelvic examination was negative except for a purulent discharge from the cervix

and urethra. The sulfathiazole was stopped after she was given 18 Gm. in four and one-half days. The following day the tenderness and rigidity increased in the right lower quadrant; however, there was no rebound tenderness. The vaginal examination was negative and did not explain the cause of the pain and temperature of 104° F. The same afternoon she developed a headache and stiffness of the neck. The physical examination now revealed a reddened pharynx and conjunctiva. The lungs and heart were negative. The abdomen was soft and the tenderness was diminished. The sedimentation rate was 18 mm. in twenty-eight minutes. The blood count was 3,200,000 red blood cells, 63 per cent hemoglobin, and 6,000 white blood cells. Agglutination tests for typhoid and typhus were negative. The urine showed a faint trace of albumin. On the same day the patient was slightly lethargic, her throat red, tongue coated, abdomen tender and rigid in both lower quadrants. The signs were now more marked. The surgical consultation on the same day, with the same findings, attributed them to a pelvic inflammation. The next day, the stiffness of the neck and headache persisted though the abdominal signs subsided. The temperature was 97.8° F., pulse 120, and blood pressure 110/80. The following day, the condition improved with only slight tenderness in both lower quadrants. Urine examination showed a faint trace of albumin and many pus cells in a catheterized specimen. On May 22, the medical consultant made a diagnosis of a right lower pneumonia. The temperature, pulse, and respiration were normal. The following day, x-ray examination of the chest was negative for consolidation and infiltration. Because of the bizarre symptoms and varied diagnoses we felt that this most likely was a drug reaction. To prove this, we decided to repeat the drug cautiously. The next day, after having taken 60 gr. of sulfathiazole headache, dizziness, nausea, stiffness of the neck, and pain in both legs returned. The temperature rose to 102° F., and the pulse to 128. The drug was discontinued and fluids were forced. The blood count was 4,830,000 red blood cells, 77 per cent hemoglobin, and 8,900 white blood cells. No sulfathiazole was present in the blood. On June 3, the legs were still stiff and the temperature, pulse, and respiration were normal. The next day all symptoms and signs subsided and the patient was discharged on June 8.

Summary

1. In a total of 904 cases treated with sulfathiazole, three cases of serious toxicity developed.

2. The first patient after receiving 20 Gm. developed toxicity on the fifth day of treatment. The second patient developed signs after 28 Gm., which was upon completion of the therapy. The third patient became toxic after receiving 16 Gm. for four days.

3. A history of liver or kidney pathology, anemia, leucopenia, and previous sensitivity to sulfonamides are contraindications to the administration of the drug.

4. The fact that only 3 cases of severe toxicity developed in a series of over 900 patients treated shows that sulfathiazole is a safe drug to use in the dosage given. This conclusion is all the more valid since two of the cases of severe toxicity could have been avoided had a more thorough history been available.

We hereby express our thanks to Dr. E. A. Horowitz for including those patients which were on his service, and to M. C. Finkel, for assistance in preparing this paper.

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THE EFFECT OF STILBESTROL ON PUERPERAL MORBIDITY AND LACTATION*

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IT IS well known that despite all preventive measures, a certain proportion of puerpera develops evidence of endometritis. Statistics vary from clinic to clinic, depending on the type of patient received and the frequency of temperature notation; but if the criteria of the joint Committee on Maternal Welfare are followed, the uncorrected morbidity in most clinics ranges between 7 and 12 per cent for white women, and possibly twice this for colored. In our own Clinic, which admits no normal multiparas to the ward service, and which receives a large number of referred complicated cases, the uncorrected morbidity for 1937 to 1940 was 10.7 per cent for white women and 20.4 per cent for the colored race, abdominal procedures being excluded. To be sure, the great number of these infections are mild and of short duration, but they nevertheless represent foci of infection from which grave types of extension may develop.

The possibility that some form of estrogenic therapy might reduce this puerperal morbidity has been suggested to the author by several facts. The well-known studies of Williams[1] demonstrated that with the exception of the placental site, the uterine cavity is completely lined with endometrium by the fourteenth post-partum day, or shortly thereafter, but the area previously occupied by the placenta does not entirely disappear until six or seven weeks following delivery. Since urinary estrogen[2, 3] is low following parturition, and since endometrial regeneration does not begin until after the usual time for the onset of endometritis, it seemed conceivable that the administration of this hormone might bring about a more rapid regeneration of the endometrium than normally occurs, with beneficial effects on the incidence of infection. It also seemed that other established effects of estrogen, such as that of maintaining a good uterine blood supply,[4, 5] increasing the tone of the myometrium,[6, 7] and sensitizing the latter to oxytocics,[6] might militate against the occurrence of endometritis.

In 1940, Connally, Dann, Reese and Douglass administered 5 mg. of stilbestrol daily to 200 puerperal women, with results which were reported in this Journal.[9] This series showed an extremely low morbidity rate, but as the group was somewhat small and rather inadequately controlled, the present continuation of that study was undertaken.

*The stilbestrol used in this study was furnished by the Abbott Laboratories.

Methods of Study

1. From Sept. 1, 1940, to May 31, 1941, every other patient delivered on the obstetric service of the Johns Hopkins Hospital received almost immediately postdelivery 5 mg. of stilbestrol in oil, by intramuscular injection. Each day thereafter, 5 mg. of stilbestrol were given orally, until the patient was discharged. Those patients delivered by cesarean section and those having abdominal operations during the puerperium (tubal ligations) were excluded from the study. Aside from the administration of stilbestrol the care given the two groups of patients was identical. Each mother in both the control and treated categories received one ampule of obstetrical pituitrin by the intramuscular route, following the second stage of labor, and one ampule of ergonovine, intramuscularly, immediately after delivery of the placenta. In addition, both groups were given 0.4 mg. of ergonovine by mouth, at four-hour intervals, until six doses had been administered. This was not repeated unless the patient became morbid. The criterion of morbidity employed was that of the Joint Committee on Maternal Welfare, namely, a rise of temperature to 100.4° F., on any two days of the puerperium (not necessarily successive), with the exception of the first twenty-four hours, temperature readings being made at 8, 12, 4, and 8 during the day and at midnight and 4 A.M., if the patient was awake.

2. During the twelve months' period from June 1, 1941, to May 31, 1942, the program of giving alternate patients stilbestrol was discontinued and a somewhat different method of study pursued. In the first two quarters of this interval no stilbestrol whatsoever was administered; during the third quarter, all patients delivered vaginally received the hormone post partum for nine days, and during the last quarter for three days.

3. Throughout the two-year investigation, every effort was made to carry on breast feeding as usual. Since most studies heretofore reported on the lactation-inhibiting effect of stilbestrol have been done on nonnursing mothers (that is, in conjunction with "drying-up" the breasts), it has seemed particularly worthwhile to observe the incidence and course of breast feeding in the present series in which maternal feeding was urged in all cases.

Results

The total number of patients studied in the first year of the investigation was 909, of which 442 fell into the stilbestrol group and 467 into the control. The results in regard to puerperal morbidity are shown in Table I. Since the incidence of febrile puerperiums in Negresses is much higher than in white women, the two races have been considered separately. Although the make-up of the control and stilbestrol groups was quite similar in respect to spontaneous deliveries, instrumentation, intra-partum infection, etc., the incidence of puerperal morbidity in the two groups was decidedly different: among Negresses the control series showed three times the morbidity of the stilbestrol group and in white women four times. The total morbidity of 5.6 per cent in the treated group, as against 20.1 per cent in the control series, would seem of definite significance.

The results of the second year's study are shown in Chart 1. In evaluating the figures for the first six months, during which no stilbestrol was administered, it should be noted that these percentages are compar-

able to those observed in the clinic in previous years when no stilbestrol was given. Thus, between 1937 and 1940 among 2,174 white patients the puerperal morbidity was 10.7 per cent, while among 2,319 colored women it was 20.4 per cent. With the resumption of stilbestrol administration in the second half of the year, a major reduction in puerperal morbidity occurred. During the three months, when it was administered to all patients for nine days, the morbidity among white women was 1.1 per cent and among the black, 5.2 per cent; during the last quarter of the year, when the administration of the hormone was curtailed to three days, the morbidity among the whites was 6.0 per cent and among the blacks 10.2 per cent.

The effect of stilbestrol on the ability of mothers to nurse their infants is shown in Table II and Chart 1. Although lactation in Negresses was found to be slightly superior to that in white women, the difference was not of sufficient degree to warrant separate consideration. Table II shows the results of the first year's experience in which stilbestrol exerted a markedly suppressing action on lactation even though attempts are made to carry out breast feeding as usual. Only 45.3 per cent of women in the stilbestrol series could nurse their infants in contrast to

TABLE I. SHOWING THE PUERPERAL MORBIDITY, AS WELL AS THE TYPE OF DELIVERY, IN 467 CONTROL CASES AND IN 442 ALTERNATE CASES IN WHICH STILBESTROL WAS ADMINISTERED POST PARTUM, 5 MG. DAILY (FIRST YEAR'S STUDY)

	COLORED PATIENTS		WHITE PATIENTS		TOTAL CONTROL	TOTAL STIL-BESTROL
	CONTROL	STIL-BESTROL	CONTROL	STIL-BESTROL		
Number of cases	235	217	232	225	467	442
Spontaneous deliveries	165	142	149	138	314	280
Low forceps OA	51	60	55	63	106	123
Low forceps OT	5	1	5	7	10	8
Low forceps OP	10	6	5	9	15	15
Breech extraction	3	7	14	8	17	15
Version and extraction	1	1	4	0	5	1
Episiotomies	81	85	90	100	171	185
Intra-partum infection	8	8	9	9	17	17
Total number of morbid cases	61	18	33	7	94	25
Total morbidity in per cent	26.0	8.3	14.2	3.1	20.1	5.6

TABLE II. SHOWING THE EFFECT OF STILBESTROL ON LACTATION IN THE SAME GROUP OF CASES AS CITED IN TABLE I

	CONTROL CASES	STILBESTROL CASES
Total number infants	485	478
Number on breast feeding only	361	217
Per cent breast-fed only	74.4	45.3
Average birth weight of breast-fed infants in grams	3,248	3,238
Average weight loss of same in grams	178	249
Average birth weight of all infants	3,198	3,180
Average loss in weight of all infants	194	266
Infants below birth weight after ninth day	237	361
Per cent below birth weight after ninth day	48.9	75.6
Inanition fever	11	49
Per cent inanition fever	2.2	10.2

74.4 per cent in the control group; the average weight loss was much greater in the stilbestrol series; in the control group only 48.9 per cent of the babies had failed to regain their birth weight after the ninth day, but in the stilbestrol series 75.6 per cent had been unable to do so; the incidence of inanition fever was more than four times as high in the stilbestrol series. Chart 2 shows the results in respect to satisfactory lactation during the second year of study. Here it may be seen that during the quarter in which stilbestrol was given for nine days, only one infant in six could be breast fed. During the last quarter in which the hormone was administered only three days post partum, the reduction in the incidence of breast feeding was less marked but was still substantial.

Vomiting rarely occurred, a fact in keeping with the belief that pregnant and puerperal women are peculiarly tolerant of stilbestrol.[10-12, 14]

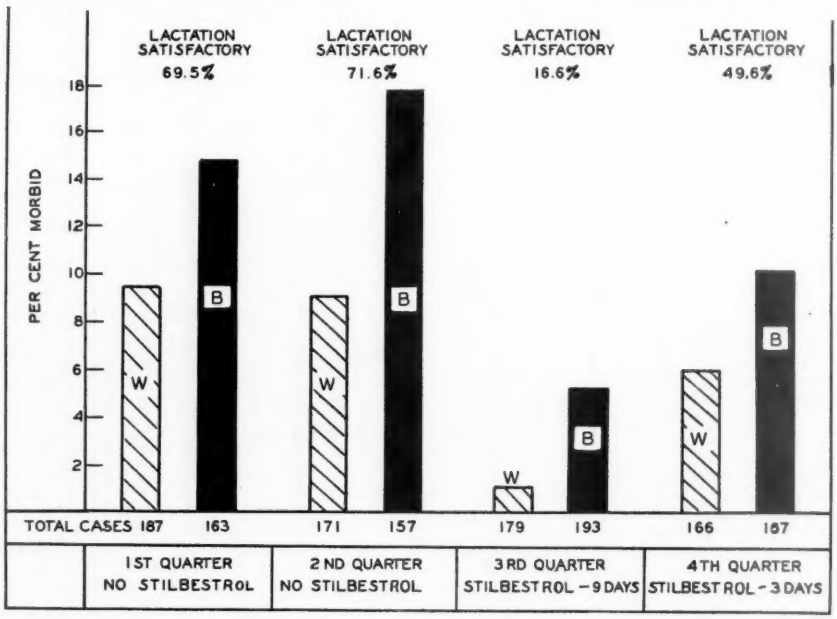

Fig. 1.—Showing the effect of stilbestrol on puerperal morbidity and lactation during the second year's study.

Comments

If it be true that the administration of stilbestrol in the puerperium reduces the incidence of febrility post partum, the observation would seem worthy of record as an endocrinologic fact. The mechanism by which stilbestrol exerts this effect is not clear but, as already indicated, the following possibilities may be speculated upon: (1) increase in uterine blood supply; (2) improvement in myometrial tone; (3) sensitization of the uterus to oxytocics; (4) increased rate of endometrial regeneration; (5) alteration of vaginal pH; suppression of mammary engorgement.

Concerning the effect of stilbestrol on the uterine blood supply, the well-known increase in vascularity of the pelvic organs prior to menstru-

ation and conversely, the ischemia which follows the menopause, attest the important role of the estrogens in this regard.

Markee's observations on the effect of estrogens on endometrial transplants likewise emphasize the action of these hormones in maintaining uterine blood supply. In 1938 Englehart[8] reported three cases of puerperal endometritis treated with estrogens and attributed the beneficial results achieved to improvement in uterine vascularity and increased myometrial tone. Wolf,[2] as well as Falls, Lackner and Krohn,[7] have shown that estrogens lend better tone to the post-partum uterus by increasing its contractility; while, in addition, Wolf observed that estrogens sensitize the myometrium to oxytocics. Very recently Rutherford[15] has demonstrated that the administration of 10 mg. diethylstilbestrol daily to puerpera hastens endometrial regeneration by 25 per cent.

Although the effect of stilbestrol on puerperal morbidity, as shown in this paper, is an interesting endocrinologic fact, the associated inhibition of lactation precludes the routine employment of this measure. Indeed, in conclusion, the author wishes to stress the fact that he is *not recommending the use of stilbestrol in the puerperium,* but is merely citing additional evidence, of academic significance only, concerning the effect of this hormone on the post-partum course.

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UNIVERSAL EDEMA OF THE FETUS UNASSOCIATED WITH ERYTHROBLASTOSIS

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FETAL HYDROPS has been recognized for many years as a condition found in a small number of human fetuses which are dead at birth or die shortly thereafter. Ballantyne,[1] as early as 1892, was able to collect 65 cases from the literature and could find no uniformity in associated maternal complications or in pathologic conditions, other than the edema, in the affected fetuses. He states that "it is impossible to frame a satisfactory definition of this fetal malady for the cases which have been recorded by various authors present differences so wide as to suggest that we are dealing, not with a pathologic entity, but with a group of symptoms common to several different morbid conditions. It may, however, for convenience be defined as a rare condition of the fetus characterized by general anasarca, by the presence of fluid effusions in the peritoneal, pleural, and pericardial sacs, and usually by edema of the placenta; and resulting in the death of the fetus or infant before, during or immediately after birth. It is to be distinguished from such conditions as ascites, or peritonitis of the fetus, edema neonatorum, congenital elephantiasis and from fetal syphilis."

Certain of his cases are definitely recognizable as belonging to the entity subsequently recognized and designated as erythroblastosis. Of one such case he says, "the liver cells were imperfectly formed, and among them were many nucleated white blood cells; and whilst these latter were not, I think, so numerous as to constitute a lymphomatous state of the liver, still I have not seen so many leucocytes in the liver of a normal full-time infant. The same remarks apply to the microscopic examination of the spleen." Of another case he remarks that "nucleated white corpuscles were everywhere present . . . in the subcutaneous tissue were many lymphoid cells."

Not many of the infants described in this series of 65 were examined at autopsy, but among them are included three with congenital cardiac defects, two with polycystic kidneys, one with a diaphragmatic hernia, one with syphilis, one with simple degeneration of liver cells, and six in which leucemia or leucemoid reactions with great increase in cells in liver, spleen, and kidney are reported. The cells designated as leucocytes are doubtless nucleated red blood cells, and in the six exhibiting such cells, it may be considered that erythroblastosis was the probable

cause of the edema. Many of the other infants, however, in all probability did not have erythroblastosis.

In the years which have followed the publication of Ballantyne's monograph, the abnormal cells in the spleen and liver have been recognized as normoblasts and erythroblasts, and the condition in which they are found associated with severe generalized edema, has been linked with certain cases of icterus gravis in which similar abnormal cells are recognized. These two clinical pictures have been included under the name erythroblastosis, and during the last fifteen years over two hundred papers have been written on the subject.

In many of these papers one finds the statement that only certain cases of icterus gravis should be diagnosed as erythroblastosis since severe jaundice may be produced by septicemia, syphilis, atresia of the bile ducts, and other conditions. Almost never, however, is there mention of the fact that there are certain cases of universal edema of the fetus which should not be included in this category. Practically all authors appear to accept all hydropic infants as suffering from erythroblastosis.

This is one of the principal reasons for the commonly found statement that infants with erythroblastosis fail to show any picture which is histologically characteristic, despite the fact that the histologic pathology was one of the principal reasons for originally combining fetal hydrops and icterus gravis as a single entity. There are some authors, however, who believe that certain histologic evidence must be present in order to make a diagnosis of erythroblastosis, and that, in the absence of these findings, the diagnosis of erythroblastosis cannot be established.

I believe that the latter view is correct and that the diagnosis of erythroblastosis should be limited to that group of infants who appear to suffer from a specific disease entity. I also believe, with Ballantyne, that fetal hydrops is not a specific disease, but only a symptom common to several different morbid conditions.

Erythroblastosis should not be diagnosed unless all of the following symptoms are present: anemia, abnormal increase in nucleated red blood cells in the peripheral blood, erythropoiesis in locations where it does not normally occur, and enlargement of the spleen. In practically all infants with this disease other abnormal findings will also be present, but without those listed above the diagnosis is always open to question. Since in infants who survive, histologic examination of the organs is impossible, the diagnosis must rest on examination of the blood and palpation of the spleen.

Neither edema nor jaundice is essential for a diagnosis of erythroblastosis but in all, except in rare instances, some degree of one or the other, and often both, is present. In infants who die soon after birth, either one may be so mild as to go unnoticed. Associated conditions

which are usually but not invariably found are mild cardiac hypertrophy, mild decrease in thymic size, marked hypertrophy of the liver, bile thrombi in the intracanalicular hepatic ducts or bile pigment or hemosiderin in the hepatic cells or Kupfer cells (irrespective of the presence of visible external jaundice). In the hydropic group, pleural and peritoneal effusions and hypertrophy of the placenta are usually present.

Clinical Material

During the course of the last several years the possibility of the existence of erythroblastosis has been considered in over 100 infants who have been subjected to postmortem examination in the laboratories of The Chicago Lying-in Hospital. This has been either in relation to clinical findings such as an abnormal blood picture, edema or jaundice, or in relation to certain abnormal conditions found at necropsy. The diagnosis of erythroblastosis has been established with a fair degree of certainty in over 50 infants; in the remainder the condition was believed not to exist.

Among those in whom the typical findings of erythroblastosis were absent, there are 17 infants with the severe edema which is characteristically described as fetal hydrops. These infants comprise a fairly uniform group and appear to be an entity entirely separate from erythroblastosis. The majority of these infants have extreme pleural and peritoneal effusions which are usually greatly in excess of amounts found in erythroblastosis. These accumulations of fluid appear to develop very early in fetal life and often produce compression of both the thoracic and abdominal viscera. The organs are frequently hypoplastic in relation to the body size even after allowance is made for the increased weight due to edema. The lungs are usually especially small.

In contrast to erythroblastosis, the spleen and liver are never enlarged and the spleen is often extremely hypoplastic. The circulating blood shows little or no increase in nucleated red blood cells and abnormal erythropoiesis is rarely visible in any organ.

The histologic appearance of the tissues shows little variation from the normal. In those instances in which the lungs are hypoplastic, the alveoli are correspondingly immature; capillary ingrowth into the alveolar wall is retarded and the original cuboidal cells lining the alveoli are proportionately more numerous than normal for the gestational age. Although the spleen is often hypoplastic, Malpighian corpuscles are well developed. This is in contrast to the findings in erythroblastosis; in this condition the lymphoid tissue of the Malpighian corpuscles is greatly reduced in amount or is entirely absent. The liver does not show the presence of pigment in the bile capillaries or hepatic cells.

Four of the infants in this group of 17 were malformed; one had a cardiac abnormality consisting of a patent atrioventricular ostium, one had multiple malformations which included a harelip, cleft palate, left diaphragmatic hernia and hypertrophy of the clitoris; one had multiple malformations the most important of which were atresia of the trachea and polycystic kidneys, and one had only a hypospadius. Two infants were twins, and although the other of each pair also died they were not edematous and the cause of death appeared to be prematurity in each case. None of our infants with erythroblastosis have been malformed.

The maternal histories show many differences from those usually found in association with erythroblastosis. With one exception (and the possibility of one other in whom record is not available) the mothers are all under 30; six are primigravidas, a condition which we have not observed (except once in a patient with numerous previous transfusions) in erythroblastosis. We have been able to acquire information concerning subsequent pregnancies in 11 of the 17 women. Five have not had further pregnancies; six have given birth to seven normal living children. There have been no subsequent unfruitful pregnancies. This is in contrast to the group with erythroblastosis; among these, 15 are known to have had subsequent pregnancies; all, with one exception, ended in the delivery of infants with fatal erythroblastosis. This one infant was jaundiced at birth but survived after receiving three transfusions.

Of especial interest are the results of the Rh determinations performed on the mothers' blood. Blood could not be obtained from six patients, but of the 11 tested *all were Rh+*. These findings are in marked contrast to those in erythroblastosis; in that condition 90 per cent of 60 patients giving birth to babies with proved erythroblastosis whose bloods were tested in the same laboratory were Rh–.

The differentiation of infants with true erythroblastosis from those who suffer from some other pathologic condition is extremely important. The discovery of the Rh factor has greatly stimulated interest in erythroblastosis and the diagnosis is being made with much greater frequency than formerly. The recognition of erythroblastosis is most desirable, but it is equally important that the diagnosis be limited to those infants who actually exhibit the characteristic pathologic picture.

The prognosis for the future bearing of normal children is very poor after a woman once gives birth to an infant with erythroblastosis. Further attempts at childbearing are in general to be discouraged, but one should be certain that the condition exists before a recommendation against future pregnancies is made. Curtailment of pregnancy because of an erroneous diagnosis produces unnecessary unhappiness in women desirous of having children. For this reason, if for no other, it should be realized that erythroblastosis exhibits a specific clinical and pathologic picture, and that both severe jaundice and generalized edema may exist in conditions other than erythroblastosis.

Summary

Marked edema of the infant may exist independently of erythroblastosis.

There appears to be a characteristic clinical and pathologic picture consisting of extreme anasarca and extreme pleural and peritoneal effusions often associated with marked hypoplasia of the lungs and spleen. There is no increase in the number of circulating immature erythrocytes and ectopic areas of erythropoiesis are absent.

The mothers are often primigravidas and all of those so far tested are Rh+.

The condition should be definitely separated from erythroblastosis because of the difference in prognosis for future pregnancies in the two diseases.

It has been observed in one infant of two pairs of twins, the other twin in each case appearing normal except for prematurity.

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ACUTE INTESTINAL OBSTRUCTION DUE TO BANDS COMPLICATING PREGNANCY*

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THE objects of this presentation are to direct attention to the serious combination of acute intestinal obstruction and pregnancy, largely because of delay in diagnosis; to outline the proper management of such cases based upon personal experience and to review the literature; and to report two cases of our own, in one of which two episodes of intestinal obstruction occurred during the same pregnancy. We have found no previous report of a similar case.

Acute intestinal obstruction has always been a serious disease but when it is complicated by pregnancy, several new factors appear which test one's judgment, particularly with regard to the diagnosis and treatment. The incidence of acute intestinal obstruction during pregnancy is not frequent. At the Woman's Hospital in New York, Bemis[3] found 2 instances among 15,000 obstetric cases, while at the Boston Lying-in Hospital from 1916 to 1938, Smith and Bartlett[9] found that among 66,431 deliveries, there were 61 abdominal complications only one of which was an intestinal obstruction. In an extensive review of the literature, Slemons and Williams[8] found that any of the causes of intestinal obstruction in the nonpregnant individual may complicate pregnancy but the most common cause is postoperative bands, between 200 and 300 such cases having been reported, the previous operation usually having been for organic pelvic disease or for removal of the appendix. They found that ileus during pregnancy was accompanied by a maternal mortality of 40 per cent and a fetal mortality of 65 per cent, the highest death rate occurring with intussusception and the lowest when the obstruction was due to a constricting band. That some progress has been made in the handling of this condition is shown by the report of Eliason and Erb,[6] who quote a series of 95 cases of all types collected by Ludwig up to 1913 with 54 per cent mortality, a series of 80 cases collected by Mikulicz-Radecki from 1913 to 1925 with 39 per cent mortality and then present their own collected series of 66 cases from 1925 to 1935 with 21 per cent mortality. All of these series show that adhesions and

*Presented at a meeting of the Philadelphia Obstetrical Society, November 5, 1942.

volvulus are the most frequent causative agents while strangulated hernia is seldom the cause, since the enlarged uterus pushes the intestine upward away from the hernial orifices.

Several authors have stated that there are three periods during pregnancy when obstruction is most likely to occur: (1) during the fourth and fifth months when the uterus ascends from the pelvis, (2) during the eighth and ninth months when the fetal head descends into the pelvis, and (3) during delivery and the early days of the puerperium when a marked change occurs in the size of the uterus with consequent change in intra-abdominal pressure. This oft-repeated statement should not be taken too seriously, however, since Hansen[7] has analyzed a series of 80 cases with respect to the time during pregnancy when obstruction occurred and found them distributed generally during pregnancy after the third month, the actual figures being 22.5 per cent in the ninth month, 17.5 per cent in the eighth, 16.25 per cent in the seventh, 11.25 per cent in the sixth, 13.75 per cent in the fifth, 3.75 per cent in the fourth, 5 per cent in the third, 8.75 per cent post partum, and 1.25 per cent in labor.

Having reviewed the American literature of the past ten years we note that most articles consist of case reports only and therefore we believe that a survey of these cases together with two cases of our own and a summary of the experience in 33 Philadelphia hospitals will be of interest at this time. While any cause of intestinal obstruction may be associated with pregnancy, we are concerned primarily with the type that is due to bands resulting from a previous abdominal or pelvic operation. We have found that the cases reported during the past ten years have occurred in almost equal numbers after simple appendectomy and operations upon the adnexa and in one case following a cesarean operation. They have occurred after any type of incision, including the McBurney, and in most of the cases no drainage had been used at the primary operation. The time interval between an operation and a subsequent obstruction varied considerably, the earliest obstruction occurring eight weeks after a previous operation. Of particular interest is the fact that in cases reported by Barone, Power and Kuhn,[2] Casagrande,[5] Weintraub and Jaffe,[10] as well as in one of our own cases, the patient had gone through a normal pregnancy between the time of the original operation and the pregnancy which became complicated by obstruction. We have found only 13 cases of obstruction due to bands reported during the past ten years. In three cases the mother died and the fetus was lost in three.

Under the auspices of the Committee on Maternal Welfare of the Philadelphia County Medical Society a request was sent to 50 Philadelphia hospitals that a search be made through their records of the preceding ten years. Thirty-three hospitals replied and using the information received together with cases gleaned from the records of the Philadelphia County Medical Society, a total of 22 cases of intestinal obstruction complicating pregnancy was found, of which 12 were ante partum.

Of these, seven were due to bands or adhesions resulting from a previous operation, death of the mother resulting in five instances and death of the fetus in six. In only one instance therefore did the pregnancy result in a living child. Obstruction followed a previous appendectomy in three instances, an appendectomy and pelvic operation in two, and an upper abdominal operation in one. In one case there was a pelvic operation without appendectomy. Obstruction occurred between the third and seventh months in all except one case in which it occurred at term. While the results in this Philadelphia series are much worse than those from the literature, none of them had been previously reported, and it should be remembered that one is more likely to report successful results than poor ones. Were it possible to get similar statistics from the country at large, it is quite likely that the results would be much worse than the reported statistics. Table I summarizes the situation as we have found it.

TABLE I. OBSTRUCTION DUE TO BANDS DURING PREGNANCY. (1932-1941)

	REPORTED IN LITERATURE	PHILADELPHIA HOSPITALS	PERSONAL CASES
Number of cases	13	7	3*
Death of mother	3	5	0
Death of fetus	3	6	1†

*Two obstructions occurred in one patient.
†Neonatal death; prematurity, immaturity, intracranial hemorrhage.

Our own experience with this condition is outlined in the following case reports:

CASE 1.—A 23-year-old white female was admitted to the Jewish Hospital on Aug. 21, 1941, complaining of cramplike epigastric pain of three days' duration, nausea and vomiting on two occasions, and during the preceding twelve hours had been obstipated. She was six months pregnant, the fetus being active and the fetal heart sounds well heard. She had been operated upon in November, 1940, for removal of the appendix and resection of an ovary. On the day before admission her habitual mild constipation seemed more marked but responded to a laxative and an enema. On the day of admission the pain was more severe and an enema was ineffectual although she passed a small amount of flatus. At this time she was quite uncomfortable on account of abdominal cramps, the temperature was 99° F., pulse 90, and respirations 20.

Urine examination was negative except for a plus 4 acetone. The hemoglobin was 86 per cent, leucocytes, 5,600, with 56 per cent polynuclear cells. The general physical examination was negative except the abdomen, which was slightly distended and tender with muscular rigidity over the upper portion. The uterus was enlarged to a size corresponding to a six months' pregnancy and peristalsis was heard, almost normal in character, over the upper abdomen and in both loins. On the following morning the symptoms persisted, the abdomen was more distended, and peristalsis was less evident. A flat x-ray film showed definite evidence of distended loops of small bowel in the right lower quadrant and laparotomy was performed about twenty hours

after admission. The obstruction was found to be in the lower ileum and was due to five bands, four of which were running from the lower ileum to the pelvis and the other was running from the ileum to the descending colon. These bands were divided and ligated and a prophylactic ileostomy was done proximal to the highest point of obstruction, since the bowel was moderately distended. After operation the patient was given morphine and progesterone to prevent uterine contractions and prostigmine to stimulate intestinal activity so that the distended loops would be less likely to adhere to each other and cause a secondary obstruction. Her convalescence was uneventful and she was discharged on the fifteenth day after operation, the ileostomy having closed and the pregnancy continuing normally.

On Nov. 21, 1941, at 1:00 A.M. she was again admitted to the hospital with some abdominal pain and vomiting, although she had had three bowel movements during the preceding day. She was treated conservatively during the night and was comparatively comfortable the next morning. She passed no flatus and later in the day her pain recurred with increasing severity, was intermittent in character and she again vomited. A flat x-ray film disclosed distended loops in the ileocecal region and the conclusion was reached that she was again obstructed. Although she was entering her last month of pregnancy, the head was still floating, and it was decided that the induction of labor would necessitate undue delay before the obstruction could be relieved. Accordingly she was submitted to laparotomy. On opening the abdomen many loops of distended intestine were found above and to the right of the enlarged uterus which were adherent to the right abdominal wall. A classical cesarean section was done by Dr. Jacob Walker, obtaining a living but premature male child weighing 5 pounds. After the uterine incision had been sutured, with of course marked reduction in the size of the uterus, the abdomen could be more readily explored. Numerous adhesions between loops of small bowel and between the small bowel and the right abdominal wall were found and divided until it was evident that all points of obstruction had been relieved and the abdomen was closed without drainage. The baby died the following morning and necropsy revealed intracranial hemorrhage. The mother's convalescence was uneventful.

CASE 2.—A 31-year-old white female was admitted to the Jewish hospital at 10 P.M. on Jan. 25, 1942, with a history of pain in the right side of the abdomen and repeated vomiting during the preceding twenty-four hours. Fifteen years previously she had been operated upon for a ruptured appendix and the wound had drained for a long time. A hernia appeared in the incision nine years ago. Since then there was an occasional throbbing in this region but the hernia was always reducible until the onset of the present attack. She had had one bowel movement in the morning but had passed no flatus since. She was in her sixth month of pregnancy which had been progressing normally. She had had two children since her operation, at eleven and nine years, respectively, before her present admission. On examination there was a tense incisional hernia in the lower right side of the abdomen, peristalsis was hyperactive, the temperature was normal, and the pulse was 104. She was still vomiting and quite apprehensive. As the result of our experience with Case 1 it was decided to operate immediately. The old scar was excised exposing a large hernial sac which was filled with adherent omentum. At first it was thought that this omentum by

angulating the transverse colon might be causing the obstruction. However, after the omentum was freed and replaced in the abdomen, examination of the right lower quadrant revealed two separate peritoneal bands, running from the terminal ileum to the parietal peritoneum below the incision. These bands were angulating and obstructing the small bowel. They were cut and the bowel released and the abdomen was closed without drainage. Postoperatively there was a slight reaction for the first day and she had a Wangensteen suction drainage applied for two days. On the fourth day she developed cramplike pain suggestive of a threatened miscarriage, but this subsided after the use of morphine. Her further convalescence was uncomplicated, and she was discharged on Feb. 6, 1942, with the pregnancy continuing normally.

Comment

The diagnosis of intestinal obstruction during pregnancy should not be difficult, but it is seldom made in the early stage. The symptoms of obstruction are pain, vomiting, constipation, and distention, in that order of frequency, but it will be readily noted that any or all of these symptoms may be present in the course of a normal pregnancy. Rhythmic pain may be equally prominent in an oncoming miscarriage as well as in intestinal obstruction, but in the former it is not likely to be associated with the other cardinal symptoms of obstruction and is often accompanied by some bloody vaginal discharge. Vomiting is, of course, quite common in early pregnancy but most obstructions occur after the fifth month when emesis is not to be expected. However, in one case reported the vomiting continued all through pregnancy up to the time that intestinal obstruction supervened, while in another case there was no vomiting at any time. Constipation and distention are so common during pregnancy that they are of little value in differential diagnosis but the presence of high-pitched tinkling peristalsis on abdominal auscultation may be of considerable aid in the obstructed case. Many cases give a history of minor obstructive symptoms during pregnancy before complete obstruction occurs. The demonstration of small bowel distention by x-ray examination is almost pathognomonic of obstruction but a negative report does not rule out the condition. The diagnosis will be made with increasing frequency provided the obstetrician thinks of this possibility in all pregnant patients who have had a lower abdominal operation, whose complaints are of more than a minor character which are not promptly relieved by minor therapy.

In a condition as infrequent as this, it is obvious that no obstetrician has had an extensive experience in its management and we must be guided by the collective opinions of those who have been confronted by this serious complication. Weintraub and Jaffe[10] offer the alliterative aphorism that pregnancy predicates pernicious procrastination in the management of this condition and they believe that until proved otherwise each case is a prima facie one of mechanical obstruction. In corrob-

oration of this they have presented 4 cases and the only fatality was in a patient not operated upon. Blair[4] divides obstruction during pregnancy into two classes: (1) those without a past history of intestinal or peritoneal trouble, and (2) those with a history of peritoneal trouble with possible operation. In either type he advocates opening the abdomen. If the case belongs to Class 2, he states that the condition causing the obstruction should be dealt with, ignoring the pregnancy; if the case belongs to Class 1, he advises emptying the uterus by hysterotomy as in these cases obstruction is usually due to pressure of the enlarged uterus on the sigmoid as it enters the pelvis. Slemons and Williams[8] state that surgical consultation is essential. They believe that there are no inflexible rules for handling the pregnancy since so many variable factors enter the field, such as the period of gestation, the type of obstruction, the intensity of the toxemia, the strength of the woman, and the likelihood of delivery before long. They state that evacuation of an advanced pregnancy, occasionally even hysterectomy, may be necessary to secure proper exposure of the pelvis. If hysterotomy is to be done, it should precede any operation on the bowel in order to avoid contamination of the uterine wound.

Discussion

In our first case the use of conservative intestinal intubation was considered before operation but was fortunately rejected since it could not have relieved more than the first point of obstruction and the patient, having five points of angulation would have been left with several closed loops beyond. Moreover the obstruction in these cases is due to the fact that the enlarging uterus pushes the small bowel toward the upper abdomen making tense bow strings of adhesive bands which ordinarily might give no trouble. So long as the uterus enlarges it is difficult to see how the progressive angulation could be relieved by intubation. In an extensive consideration of intestinal obstruction from both the clinical and experimental aspects, Aird[1] states that he has been impressed by more than one case of adhesive obstruction, treated by suction drainage and saline infusion for twenty-four hours or more, only to present at operation a strangulated and devitalized bowel. The twenty-four hours of delay may mean the difference between viability and gangrene. It is conceivable to him that while the present vogue for prolonged preoperative decompression and saline administration may be expected to reduce the mortality of simple intestinal occlusion, it may actually lead to an increase in the mortality of intestinal strangulation. Even in simple occlusion of the bowel, patients still die with sufficient frequency to make him feel that we have yet something to learn of the lethal mechanism of the disease.

In our second case it might have been logical to assume that the incarcerated omentum in the incisional hernia caused obstruction by its trac-

tion on the transverse colon. Had the operation been terminated after the release of the omentum the patient would not have been relieved. The obstruction was in the lower small bowel due to bands which were found only, after the omentum was replaced, within the abdomen. This demonstrates the importance of a thorough search for multiple factors in such cases and undoubtedly our experience in the first case guided us in the operative management of the second.

Summary and Conclusions

Acute intestinal obstruction is an uncommon but serious complication of pregnancy. One of the most common causes of obstruction during pregnancy is the presence of adhesive bands resulting from a previous lower abdominal operation which become taut as the enlarging uterus pushes the intestine into the upper abdomen. Obstruction may occur at any interval after an abdominal operation and the fact that a patient goes through a normal pregnancy after such an operation is no assurance that she will not become obstructed during a subsequent pregnancy. The presence of mechanical obstruction should be suspected in any pregnant patient who has had a previous lower abdominal operation and who presents the obstructive triad of cramplike pain, vomiting, and obstipation. If x-ray examination shows distended small bowel the diagnosis is made, but negative x-ray examination does not rule out the diagnosis. The proper management of this condition consists of early operation to release the obstructing bands, making a thorough search until all points of obstruction have been released. Conservative intestinal intubation should not be used in this condition. Two cases have been presented in one of which two separate episodes of intestinal obstruction occurred during the same pregnancy.

We wish to thank Miss Malkiel, Secretary to the Maternal Welfare Committee of the Philadelphia County Medical Society and the various hospitals whose cooperation greatly assisted in the preparation of this paper.

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Discussion

DR. J. WALKER.—It is important for the obstetrician to realize that intestinal obstruction, although a rare complication of pregnancy, carries a high degree of risk for both the pregnant woman and the fetus. Much of this increased risk is un-

doubtedly due to the difficulty of early diagnosis, since, as the authors have indicated, the signs and symptoms of intestinal obstruction, distention, vomiting, abdominal pain and constipation, are commonly encountered during pregnancy as functional states, and the obstetrician is thus prone to ignore them until the picture of obstruction is dangerously well developed.

The incidence of this complication is quite low, being variously quoted as 1:15,000 to 1:68,000 cases. In my own experience, embracing over 8,000 private patients, I have encountered only two cases. The first patient was a 25-year-old primigravida who had a spontaneous rupture of the membranes at term, without labor pains. Thirty-five hours later uterine contractions began, and the physician ordered an x-ray examination, multiple pregnancy being suspected. The x-ray revealed a single term fetus, breech presenting. The pelvis was platypelloid with a true conjugate of 9 cm. I was called in consultation and performed a cervical cesarean section (Kroenig) six hours after the onset of labor, membranes having been ruptured for forty-one hours. The patient had an apparently normal postoperative course for three days, whereupon mild upper abdominal distention with high-pitched tinkling peristalsis began to appear. Although intermittently relieved, by gastric lavage, this was progressive. On the sixth postoperative day, distention was well marked. Dr. W. O. Abbott was called in consultation, and after unsuccessful efforts to pass the double-lumen tube, he advised operative relief of the distention rather than further delay. Barium enema had demonstrated obstruction at the sigmoid flexure, with distention above this point. Dr. Rothschild performed a transverse colostomy, and four days later, the fourteenth post-partum day, the patient's condition permitted abdominal exploration. An inflammatory process involving the posterior surface of the left broad ligament, posterior surface of the uterus, rectum, and sigmoid was found, and as the sigmoid was freed, a small amount of pus was evacuated. This procedure relieved the obstruction, and five days later closure of the transverse colostomy was carried out. Following a stormy convalescence the patient was discharged recovered, approximately seven weeks after the cesarean section. My second case was one of those described by Dr. Block.

What lesson are we to learn from this study? It does teach us to suspect intestinal obstruction when the abdomen bears a scar, with or without a history suggesting intermittent partial obstruction. Furthermore, this and other surgical complications of pregnancy warn us that the obstetrician should have had basic training in the handling of surgical problems; that he should remember that the enteric cavity contains more than a uterus and fetus, and that he should not hesitate to call for the aid of an experienced surgeon when signs or symptoms of a bowel lesion appear.

Binet, L., and Strumza, M.-V: Contributions to the Study of Shock, Presse méd. **48**: 825, 1940.

The writers, using 64 dogs, produced variable grades of shock by giving the animals intravenous histamine bichlorhydrate (2.5 mg. per kg. body weight). They recorded then the blood chemistry, the kymographic tracings of blood pressure, and the hematologic findings in these animals.

They conclude that serious shock is primarily a condition requiring urgent hydration as a therapeutic measure. The results they obtained in the animals suggest that, in the milder cases of shock, saline, sodium bicarbonate and hyposulfite solutions were satisfactory while the more serious cases gave promise of better results when diluted blood was used. Of interest was the observation upon the use of propionylcholine perchlorate in the treatment; in animals, return from histamine shock was usually effected in two or three hours. The dosage of this drug was 3 mg. per kg. administered very slowly, by the intravenous route.

CLAIR E. FOLSOME.

DIAPHRAGMATIC HERNIA AS A CAUSE OF "INTRACTABLE HEARTBURN" OF PREGNANCY

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THE surprising incidence, or rather, the greatly increased frequency of diagnosis, of diaphragmatic hernia in the past two decades has occasioned a large number of papers on the general subject.[1] Those roentgenologists who have become "diaphragmatic hernia minded" have been able to solve many a knotty diagnostic problem by the demonstration of such a hernia. Obscure symptoms referable to the gastrointestinal tract, the biliary system or the cardiorespiratory system have disappeared following surgical repair of anatomic defects in the diaphragm. It has been estimated[2] that under conditions of general practice, symptoms sufficient to bring patients to the roentgenologist for gastrointestinal examination will lead to the discovery of diaphragmatic hernia in roughly two out of 100 patients.

However, when dealing with the pregnant woman, the incidence of hiatus hernia appears to be much higher than this. Rigler and Eneboe[3] examined 195 women during the third trimester of pregnancy. Of 116 multiparas examined, hiatus hernia was demonstrated in 21 (18.1 per cent); in 79 primiparas, 4 were found (5.1 per cent). The combined incidence was 12.8 per cent. Of 10 positive cases re-examined after delivery, the hernia could be redemonstrated in only 3 patients. Great care was taken to distinguish between diaphragmatic hernia and regurgitation into a dilated esophagus. An attempt was made at correlation between gastric symptoms reported by these patients and the presence or absence of a hernia. No such correlation could be determined. On the contrary, there seemed to be a greater tendency to pyrosis and gastric distress in those individuals who showed simple regurgitation into the esophagus.

On the other hand, Diddle and Tidrick[4] have reported a patient who died during the first stage of her fourth labor from strangulation of the viscera in a diaphragmatic hernia and have found four similar fatal cases in the literature. It is apparent that a diaphragmatic hernia in a pregnant woman must be considered as potentially dangerous, especially when portions of the abdominal viscera other than the stomach are included in the hernia.

It is well known that diaphragmatic hernia can cause symptoms[5] resembling those caused by peptic ulcer or gall bladder pathology, often somewhat atypical, and often exaggerated upon assuming the recumbent position. Prolonged histories of slight dysphagia or pyrosis,

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unexplained anemias,[6] or anomalous cardiac symptoms, frequently postprandial and relieved by vomiting but not by food, have been symptom complexes solved in certain instances only by the discovery of an hiatus hernia. This protean nature of the clinical picture led Hedblom[7] to state: "The etiology of diaphragmatic hernia is often obscure, its pathologic anatomy diversified, and its clinical manifestations manifold."

Even though it is admitted that an appreciable percentage of diaphragmatic hernias may be symptomless, it would seem strange not to find symptoms of such a functional and anatomic defect as this, shown as it is to be unusually common in the pregnant woman. One would expect such symptoms in particular to be precipitated during the stress and strain of labor.

Reports of such complications are not common. A case is recorded[8] of emesis of blood twice during a twenty-seven-and-one-half-hour labor in a patient without previous gastric symptoms. Labor was terminated by forceps. Occasional heartburn after delivery led to roentgenologic examination of the stomach which revealed one-fourth of this organ above the diaphragm.

DeLee and Gilson[9] report the partial strangulation of the viscera in a diaphragmatic hernia during the puerperium. This case was apparently not checked by roentgenologic examination.

Evans and Bouslog[10] have recently reported four cases, termed "intractable heartburn of pregnancy," and characterized by severe epigastric distress or burning, appearing after the twentieth week of pregnancy, unrelieved by the usual gastric medication and usually aggravated by the recumbent position. Following delivery, the distress disappeared promptly and the herniation causing it could not be again demonstrated.

In all probability, diaphragmatic herniation of part of the stomach in the pregnant woman is responsible for more epigastric distress and pain than is realized. In retrospect, it is easy to recall an occasional patient who did not respond to the usual gastric remedies and in whom adequate roentgenologic study might have revealed an hiatus hernia. The tendency is to ascribe these symptoms to aberrant function, or to enlargement of the uterus with a resulting mechanical displacement of the abdominal viscera. This view is encouraged by the disappearance of distress post partum.

The possibility that this might be a relatively frequent but often undiscovered symptom correlation justifies the publication of the following case.

Case Report

Mrs. B. McC. (No. 2186), born Aug. 3, 1917, was first seen in the present illness on Nov. 25, 1941. The patient's last menstrual period had occurred Sept. 20, 1941, and she complained of nausea, pain in the back, and headaches. Onset of menses had occurred at approximately twelve years of age and had been somewhat irregular with a duration of five to seven days. A first pregnancy had resulted in miscarriage (said to have been spontaneous) at two months in May, 1938. Curettage was performed for retained placental tissue at Springfield (Illinois) Hospital. A second pregnancy terminated in the spontaneous delivery

of a living male infant after a nineteen-hour labor. Gestation and puerperium were apparently uneventful. The past medical history included measles, mumps, chickenpox, and pertussis as a child. No serious illness had ever occurred. The family history was negative.

Fig. 1.—Film of the case reported, taken in a moderate Trendelenburg position, and revealing a portion of the stomach above the diaphragm and passing through the esophageal hiatus.

Upon physical examination, the weight was 134 pounds and blood pressure 124/70. Urine examination was negative (and subsequently remained so). Head, chest, abdomen, and reflexes were normal. The blood Kahn and Eagle were both negative. The perineum had been markedly lacerated. The cervix was moderately lacerated, ulcerated and nodular. The fundus was softened and slightly enlarged. Adnexa were negative to palpation.

The course of the pregnancy was for the most part uneventful. Life was noticed about Jan. 21, 1942. Blood pressure dropped to 85/50 and remained low. During the first part of March, 1942 (approximately the twenty-third week), a moderately severe but intermittent epigastric pain appeared. Within two weeks the pain had become more constant, bore no constant relationship to food and seemed to be aggravated by lying down. It would awaken her at night and often would be relieved by assuming the erect position. Nausea was infrequent and the relatively few vomiting attacks did not always bring relief. Belching would relieve only at times. Various antacids and gastric sedatives were tried without relief. By May 6, 1942, the uterus was 6 cm. above the umbilicus and the head engaged. The blood pressure was 82/50. The weight had remained at about 143 pounds for several weeks. Roentgenologic examination (Dr. D. M. Sirca) on May 8, 1942, revealed an hiatal hernia (Fig. 1). This film was obtained in the moderate Trendelenburg position. Further fluoroscopic observation identified gastric mucosa above the diaphragm.

During May, 1942, the pain at times was quite severe and the patient was unable to obtain adequate rest at night. Because of the increasing severity of symptoms, induction of labor was advised and the membranes were ruptured artificially at 5:45 P.M. on May 26, 1942, in St. John's Hospital (Springfield, Illinois) about one month ahead of term. Sporadic contractions occurred next day and during the evening of May 27 the patient had an emesis of coffee-groundlike material. Labor began definitely about 2:00 A.M. on May 28. During the ensuing morning, two further emeses occurred, both made up largely of dark brown blood. At 12:30 P.M. on May 28, 1942, a living male child, weight 5 pounds 14 ounces, was delivered spontaneously. The puerperium was marked by the disappearance of all epigastric pain by the fourth day and the patient since has remained symptom free. Strenuous efforts to demonstrate the hiatus hernia roentgenologically three weeks post partum were unsuccessful.

Conclusions

1. Diaphragmatic hernia is being diagnosed with an ever increasing frequency and has been proved to be the cause of a wide variety of symptoms.

2. Under conditions of general practice, symptoms sufficient to bring the patient to the roentgenologist for examination will reveal a diaphragmatic hernia in about two out of 100 patients.

3. It has been pointed out that "intractable heartburn" of pregnancy, appearing after the twentieth week, unrelieved by the usual gastric medication and usually aggravated by the recumbent position, may well constitute a rarely recognized symptom of diaphragmatic hernia.

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ON THE EMPLOYMENT OF OCTOFOLLIN FOR THE RELIEF OF MENOPAUSAL SYMPTOMS, FOR THE SUPPRESSION OF LACTATION, AND IN GONORRHEAL VAGINITIS

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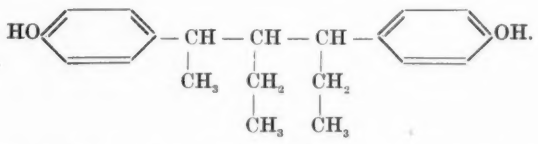
(From the Gynecological and Obstetrical Service of the Boston City Hospital)

ONE of the most important advances in the field of estrogen therapy in recent years was the discovery that synthetic chemical compounds, structurally unrelated to the natural occurring steroid hormones, were sufficiently estrogenic and free from toxicity to warrant their clinical use. These compounds had the advantage of being effective when administered orally. Since 1938, when Dodds, Lawson, and Noble[1] reported the high estrogenic activity of diethylstilbestrol, many reports of its use have appeared in the literature. A recent review by Morrell[2] and the report of the Council on Pharmacy and Chemistry[3] would seem to make an extensive reference to this literature unnecessary here.

Although permanent damage has never been established on the basis of blood, urine and liver function tests, the incidence of untoward side reactions following the administration of diethylstilbestrol cannot be completely ignored.

I wish to report my results with a new synthetic estrogen, not a derivative of stilbestrol, with which I have done extensive clinical work. The compound has the trade name Octofollin,* and is a 2,4-di(para-hydroxyphenyl)-3-ethyl hexane. It has the following chemical configuration.



It might be mentioned here that it is impossible to write this chemical formula in any way to resemble the natural estrogen, as could be done with diethylstilbestrol. Clinical results upon a selected group of menopause patients treated with this substance, then called 118 B, have been reported by Freed, Eisin, and Greenhill.[4, 5] The chemical researches leading to the development of this estrogen and the physiologic work demonstrating its efficacy and safety have been reported.[6-8]

*Product of the Research Laboratories of Schieffelin & Co., New York.

Material and Results

Octofollin was employed in this series of cases in tablets of 0.5, 1, 2, 5, and 10 mg. and in suppositories containing 1 mg. each.

The patients have been for the most part from the clinical services of the Boston City Hospital, with the addition of seven menopause cases from the private practice of Dr. John T. Williams. The results on 87 patients are given here, and are grouped according to the condition for which they were receiving treatment.

Menopause.—Fifty-three patients are reported upon and may be divided into two groups, natural and postoperative. Dosage ranged from 1 to 40 mg. daily. Because of this extreme range it is impossible to present these data in tabular form as did Freed. The results can be summarized best in the following manner:

Natural menopause: Of these 37 patients, 24 reported complete relief of symptoms on dosages of 1 to 20 mg. daily. Ten patients reported no relief, or no appreciable relief on 1 to 40 mg. daily. Some of these latter group might have obtained relief on higher dosages. Of these 10 patients, 5 were extremely refractory to any estrogen therapy, receiving no relief from theelin injections (2,000 I.U. 3 times a week) or from stilbestrol in tolerable doses. One of these patients subsequently was relieved by psychiatric therapy. Three patients reported considerable relief on higher dosages and are of course included in the first group of 24.

In but two cases was treatment stopped because of nausea and vomiting, and these patients were both receiving but 1 mg. of Octofollin daily. Short episodes of slight nausea, of doubtful origin in some instances, were reported by ten patients. All of these cases obtained relief on daily dosages, in many instances considerably higher than those at which their nausea had appeared.

Artificial menopause: Of these 16 patients treated with Octofollin, 9 reported complete relief of symptoms, which in 6 cases had been classified as severe, on levels of 2 to 10 mg. daily. Two patients reported considerable relief on 2 to 10 mg. daily, and 5 patients experienced no relief with daily dosages of 2 to 40 mg. daily. One of these 5 patients received no relief from any estrogen therapy and but one, slight relief from theelin injections. Slight nausea was reported by but one patient and therapy was not discontinued in any case because of side reactions.

Unpublished clinical data suggested that the postoperative menopausal symptoms might be harder to control than those arising during the course of the natural climacteric. In this series this did not prove to be the case. The percentage of complete relief was about the same in both groups, and while they are too small for accurate statistical calculation, the dosage level in the artificial menopausal group was the lower.

These results for the entire menopausal group show a higher level of effective dosage than that reported by Freed and his co-workers. It is recognized that this group of patients was smaller and considerably less homogenous than their carefully selected assay group. It is felt also that the average daily dose when calculated for the entire group, about 8 mg. daily, is toward the high side, because of seven patients receiving 20 mg. daily and one receiving 40 mg. daily. If these 8 refractory cases are excluded from the calculation, the average daily dose is 5 mg. daily.

While Octofollin is available in oil for parenteral administration it was not used during this study, and it is entirely possible that some of the patients reporting slight relief, or no relief with very high dosage, might have obtained some response to injection therapy.

Suppression of Lactation.—Twenty post-partum women in whom for various reasons, it was deemed advisable to suppress lactation, were treated with Octofollin. Fifteen milligrams daily (5 mg. t.i.d.) were given for four days beginning by preference on the first post-partum day. Excellent results were obtained in all cases, even those in whom therapy had not begun until milk was present. There were no toxic symptoms.

Gonorrheal Vulvovaginitis.—Fourteen little girls, ranging in age from 8 months to 5 years, were treated orally and topically with this estrogen. In the first series prior to the availability of suppositories, 4 children were treated with Octofollin tablets, 2 mg. daily. In the second group 10 children were treated with suppositories containing 1 mg. of the active estrogen, receiving one suppository three times a day. Excellent and similar results were obtained in both groups. Smears became negative for gonococci by the end of one week of treatment, and vaginal discharge and itching disappeared by the end of the third or fourth week. Slight mammary enlargement, which regressed following cessation of therapy, was noted in two cases, both on suppositories.

Discussion

Two aspects of these data may warrant mention.

First: The cases in the menopausal series were not selected with the idea of assaying Octofollin. As a matter of fact several extremely refractory patients who had shown little, if any, relief with other estrogens, theelin, estradiol benzoate, and stilbestrol were deliberately included. Several of these women, in whom control of symptoms could not be established with stilbestrol because of the onset of nausea and vomiting, were controlled by the use of Octofollin without the gastrointestinal reactions. This would seem to give specific support to the impression that, at the effective levels, Octofollin is considerably less toxic than diethylstilbestrol, and dosage can, therefore, be pushed up to levels where satisfactory symptomatic control is obtained.

Second: It was noted that once relief of symptoms had been obtained the dosage could be decreased in the majority of cases to levels one-fourth to one-half that at which the symptoms had disappeared.

The above considerations, as previously mentioned, make it difficult to state an "average daily dose" which will control the menopause. The effective therapeutic dose varies with the patient and must be individually controlled.

It might be mentioned further that these results bear out the general impression that the menopause clinic groups, particularly in the large charitable institutions, seem less favorable test groups than the more intelligent and reliable private patients. In 6 of the 7 private patients in this study in whom satisfactory results were obtained, the dose was 1 to 3 mg. daily.

Summary

The synthetic estrogen, Octofollin, which is unrelated to stilbestrol, has been given extensive clinical trial in 87 patients suffering from the various conditions for which estrogens are regularly indicated. Excellent results were obtained.

This compound is an effective estrogen and at the clinically effective levels seems to be less toxic than diethylstilbestrol.

I wish to acknowledge my thanks and appreciation to Dr. John T. Williams, Surgeon in Chief, Gynecological and Obstetrical Service, Boston City Hospital, for his help and cooperation in the writing of this paper.

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EARLY PSEUDOMYXOMA PERITONEI IN A CASE OF FETAL MECONIUM PERITONITIS*

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(From the Department of Pathology, Woman's Medical College)

THE following case is pathologically rare, and an even rarer cause of dystocia.

The mother, a 29-year-old white woman, gave no history of past illnesses. She had had two previous normal pregnancies. The present pregnancy was uneventful until the seventh month, when the patient developed edema of the ankles and vulva and frequent headaches. About the beginning of the eighth month the patient also complained for some days of severe pain in the right lower quadrant radiating to the back. The urine tests showed only occasional faint traces of albumin. There was a moderate anemia with 3,400,000 red blood cells and 67 per cent hemoglobin (10 Gm.). Blood pressure was normal. Wassermann was negative. Delivery was due Aug. 17, 1941. On August 2 the patient was seen at the prenatal clinic complaining of diarrhea, abdominal cramps, and general discomfort. At this time the abdomen was found rounded and huge, the head floating (R.O.P.), fetal movements present, and fetal heart normal. Cervix admitted one finger. A tentative diagnosis of polyhydramnios was made.

On August 9 at 10 P.M. there was an onset of laborlike but noncontinuous pains. The following day at 6 A.M. partial rupture of the membranes occurred. Regular labor pains started two days later, on

*Presented at a meeting of the Philadelphia Obstetrical Society, January 7, 1943.

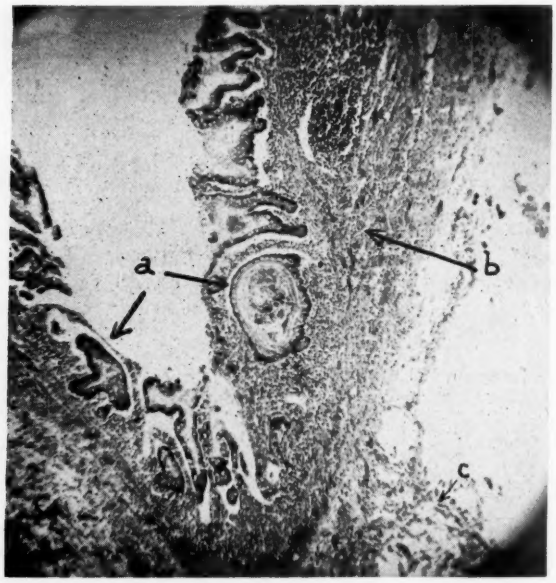

Fig. 1.—Section above perforation. Note (*a*) irregular and cystic glands, (*b*) irregular and thin muscular coats, and (*c*) adhesions.

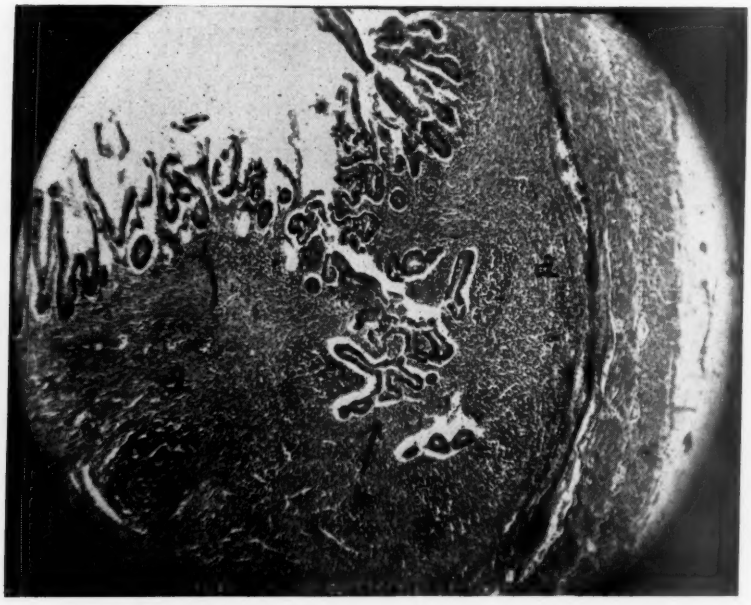

Fig. 2.—Section above perforation. (*a*) Mass of hyperplastic lymphoid tissue partly cutting off; (*b*) a group of abnormally deep glands.

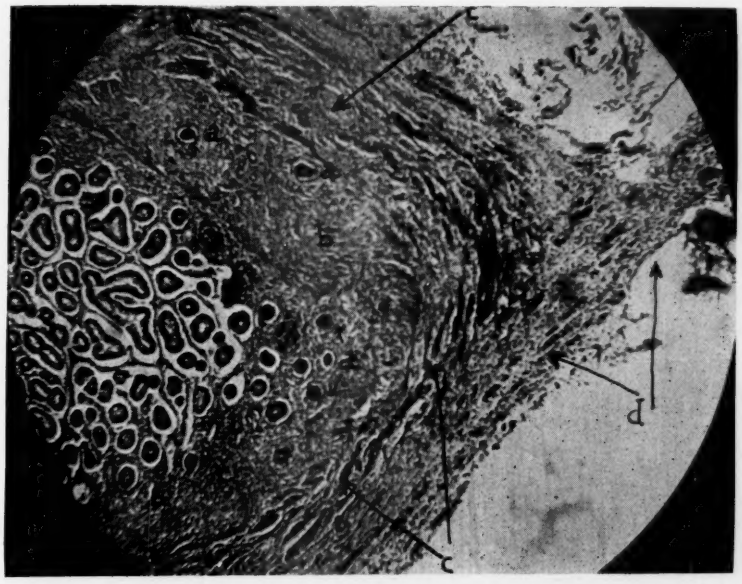

Fig. 3.—Section near perforation. (*a*) Intestinal glands penetrating in (*b*) submucosa showing fibrosis, (*c*) numerous gaps in muscular coats, and (*d*) adhesions.

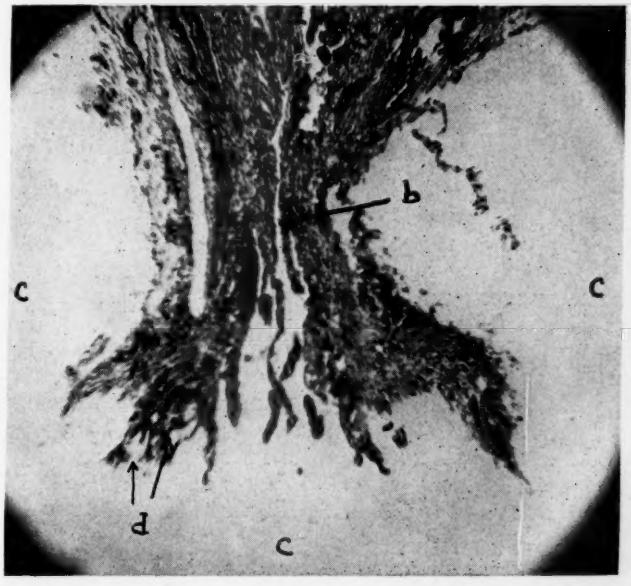

Fig. 4.—Perforation. (*a*) Lumen, (*b*) perforation, (*c*) peritoneal cavity. Note (*d*) intestinal glands opening in the peritoneal cavity.

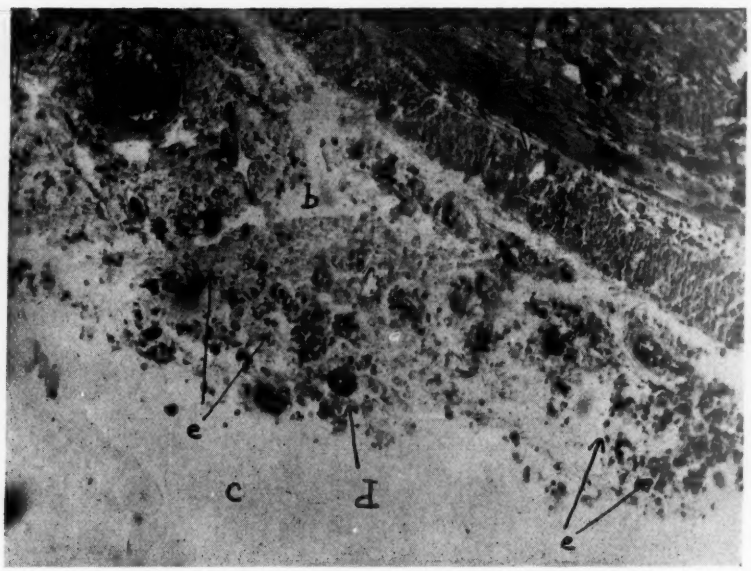

Fig. 5.—(*a*) Muscular coats of intestinal wall, (*b*) adhesions, (*c*) peritoneal cavity. Note (*d*) a well-preserved intestinal gland implanted on the serosal surface. (*e*) Inflammatory cells and pigment-carrying histiocytes.

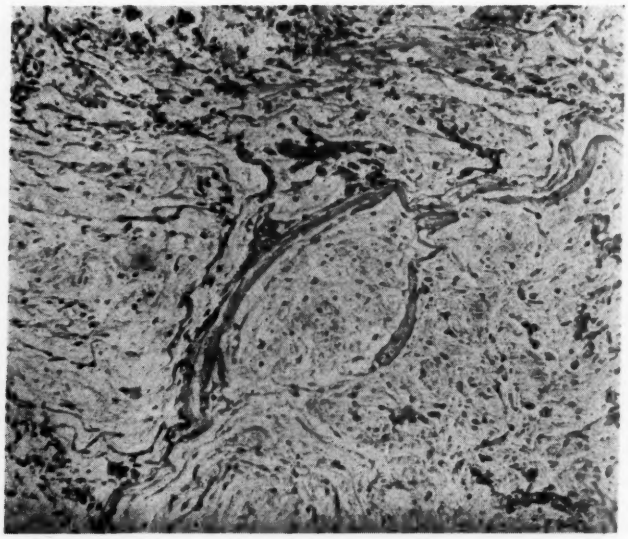

Fig. 6.—Pseudomucinous mass. Note trabeculae of fibrous tissue, stellate cells separated by mucoid material, calcified masses (lower right).

August 12 at 3 A.M. At 11:55 A.M. the head was engaged and at 12:55 the second stage was terminated by Simpson low forceps. The head was delivered with moderate difficulty, but great difficulty was encountered in delivery of the shoulders and of the abdomen which was greatly distended. The baby, a male, was deeply cyanotic. The breathing was limited to a few gasps; the heart beat ceased shortly after delivery.

Following delivery of the child about one gallon of amniotic fluid poured out.

Autopsy showed the body of an apparently full-term baby, weighing 3,980 Gm., and presenting extreme cyanosis. The abdomen, greatly distended, was 40 cm. in circumference at the navel. Fluctuation was very evident. No other abnormalities were found on external examination. The thoracic organs showed extreme congestion.

Abdomen.—The different layers of the anterior abdominal wall were edematous and congested and showed numerous small hemorrhages. The abdominal cavity contained about 300 c.c. of slightly cloudy straw-colored fluid. The greater part of the small intestine was matted together by organized adhesions which fixed it in the right iliac fossa. The ascending and transverse colon were also partly covered by adhesions, while the omentum was retracted and rolled up.

Careful separation of the adherent intestinal loops showed a greenish jellylike mass with white opaque areas about 2 by 1.5 cm. firmly adherent to the outer wall of the terminal ileum, opposite the mesentery, about 10 cm. from the ileocecal valve. The serosa covering most of the small intestine and part of the colon was thickened and opaque. Stomach, liver, and spleen were free from adhesions. The lumen of the small intestine was patent throughout, but narrower below the point to which the mucoid mass was attached. At this point the mucosa presented an infundibular depression. No gross perforation was found.

All other organs showed extreme congestion and small hemorrhagic foci. The cause of death was ascribed to asphyxia during prolonged labor.

Serial microscopic sections of the segment of small intestine to which the mucoid mass was attached revealed numerous abnormalities: several glands of the mucosa were dilated and cystic. In other places there were hyperplastic masses of lymphoid tissue, apparently cutting off groups of intestinal glands. The submucosa showed marked fibrosis and contained inflammatory cells. In one place numerous glands were scattered deep in the submucosa and surrounded by fibrous tissue. The muscular coats were very irregular in their structure and presented numerous gaps. At a point near where there were groups of abnormally deep glands, a perforation was found. The intestinal mucosa was redundant in this area and seemed to have herniated through the gap in the wall. At the site of the perforation, the intestinal wall consisted mostly of fibrous tissue infiltrated with mononuclear cells. Some isolated well-preserved tubular glands could be seen in the surrounding fibrous adhesions, together with inflammatory cells, pigment-carrying histiocytes and small calcified masses. The mucoid mass described grossly showed thin trabeculae of fibrous tissue between which were a number of stellate connective tissue cells separated by abundant intercellular substance which gave the reaction of mucin. There also were mononuclear inflammatory cells, histiocytes loaded with yellow-brown pigment, and masses of calcified material.

This is a case of the so-called fetal meconium peritonitis, that is, a "chemical and foreign body peritonitis occurring during intrauterine

life as the result of abnormal communication between the bowel contents and the peritoneal cavity'' (Boikan). In this case the presence in the peritoneal cavity of living and secreting intestinal glands accounts for the presence of the mucoid mass. The condition is comparable to pseudomyxoma peritonei following rupture of a mucocele of the appendix.

I believe that in this case the underlying cause was a developmental abnormality consisting of abnormally deep groups of intestinal glands and of a congenital weakness of the muscular coats. Some of the deeply situated glands being partly cut off from the mucosal surface may gradually have become cystic and finally ruptured into the peritoneal cavity through one of the gaps in the muscular coats. This would account for the perforation of the gut and the spilling of meconium into the peritoneal cavity.

EXTENSIVE HYDATIDIFORM MOLE FORMATION WITH LIVING CHILD

H. E. Bowles, M.D., Honolulu, Hawaii

CASES of twin pregnancies have been reported in which one ovum developed normally while the other formed a hydatid mole. We are concerned here, however, with the disturbance of a single ovum. Novak[1] believes that the hydatidiform mole is a neoplasm rather than a structure resulting from degenerative changes. Since chorionepithelioma, a truly malignant neoplasm, follows from 2 to 10 per cent of hydatidiform moles, this view seems logical.

Greenhill[2] has stated that a fetus is seldom found where a hydatidiform mole is present. This seems to be the view generally held. In 9,501 deliveries at the Queen's Hospital, Honolulu, from 1932 to 1941 inclusive, there was only one recorded instance of a single ovum with coexisting fetus and hydatidiform mole. This was in a multigravid Filipina of 27 years who delivered large masses of grapelike material and a macerated fetus of four and one-half months. Histologic examination revealed the typical picture of hydatidiform mole. Williams[3] reported in 1918 that no instance of viable fetus had been found together with hydatidiform mole formation of the placenta in 17,930 obstetric cases treated in the Johns Hopkins Medical School. Meyer[4] has made a careful study of a large series of hydatidiform moles in the Carnegie Institute of Embryology, which suggests that the occurrence of an embryo in a mole is not very rare. In this large collection of hydatidiform moles, 64.4 per cent contained fetuses in an excellent state of preservation and of an average age of 66.6 days.[5] In an otherwise normal pregnancy and delivery with a living child, it is not unusual to note small areas of mole formation. Several reliable writers (Hertzler,[6] Frank,[7] Playfair,[8] Adami[9]) have attested to this. Hirst[10] remarks that if the disease does not begin until after the villi of the chorion laeve have atrophied, or if the degeneration is confined to a comparatively limited area, the pregnancy usually proceeds to term or to the point of nonviability of the fetus. Titus,[11] Greenhill[2] and DeLee[12] confirm this statement.

A careful search of the medical literature available here in Hawaii yields an account of only one fairly authentic case of hydatid mole formation of the placenta accompanied by the birth of a living child.[5] This specimen filled a two-liter jar and was said to have accompanied a living seven months' fetus which was expelled between the time of passage of the fetus and the placenta. Unfortunately the placenta was not saved. No notes are appended as to how long the fetus survived. No doubt there have been other, unreported, cases similar to the aforementioned one.

A case recently came under our care and we have been sufficiently impressed by its rarity to feel justified in the following review.

Case Report

Mrs. G. J., aged 18 years, was admitted to the Kapiolani Maternity Hospital on Sept. 23, 1942, not in labor, at seven and one-half months of her second pregnancy. The pregnancy had been uneventful until two weeks previously at which time moderate albuminuria and beginning pitting edema of both ankles was noted. There were no headaches nor vertigo and blood pressure was 114/78. A salt poor, high protein diet was advised. In addition, ammonium chloride, grains 15, was given thrice daily. Albuminuria and pitting edema progressed however, and in addition hematuria set in and hyaline and granular casts began to appear in the urine. There was also a weight gain of eight pounds in nine days. Despite a normal blood pressure there were no headaches or dizzy spells. Other laboratory data were as follows: Red cell count 4.19 million, hemoglobin 78 per cent. Blood clotting time was six minutes; blood type was A. Blood Wassermann and Kahn were negative. Unfortunately no blood serum protein determinations were made. In view of the subsequent findings in this case, it should be noted that there was no vaginal bleeding before the time of her delivery.

This patient had been delivered one year previously, at the age of 17, of a stillborn macerated fetus at seven months. The labor had begun spontaneously and was preceded by high blood pressure, albuminuria, and generalized edema. The age of the fetus was estimated at about 6½ months. The placenta was noted at the time by the physician who delivered her to have been "dull gray and fibrotic on three quarters of its surface." No histologic study of the placenta was made and the blood Wassermann was not done at that time. Convalescence was uneventful. There were no other noteworthy points in her past history nor in the family history.

With her present admission (her second pregnancy), generalized edema was noted, with marked pitting of her lower legs and feet. The blood pressure was 120/70 and the urine showed 3+ albumin, 1+ red blood cells, and no casts. Fetal heart tones were of good quality, 160 per minute, and loudest one inch below and to the left of the umbilicus. After three days of rest and ammonium chloride therapy, with high protein and salt poor diet, it was felt advisable to induce labor, bearing in mind the loss of her first baby in the seventh month under similar circumstances. Uterine contractions were induced readily by the administration of castor oil, an enema, and repeated small intramuscular injections of pituitrin. Vitamin K was given intramuscularly at the onset of labor. After four and one-half hours of uneventful labor, during which time no sedatives of any kind were given, a well-developed though small

female infant was born normally and cried at once. Almost immediately two translucent vesicles slightly larger than peas emerged from the vagina. The cord was clamped as soon as it ceased pulsating. Palpation of the uterus revealed a cylindrical enlargement occupying its entire right side. The presence of a twin was suspected. Confusion was added by the occurrence of a furious hemorrhage, total blood loss being estimated at 1,500 c.c. The patient received 1,000 c.c. of 5 per cent glucose solution at once and 500 c.c. of whole blood soon after. In the meantime the operator removed several huge masses of grapelike vesicles from within the uterus. The severed umbilical cord emerged from typical hydatid mole tissue and there was virtually nothing present in this mass which grossly resembled placental tissue. The amount of molar tissue together with the umbilical cord removed at this time weighed 4 pounds 2 ounces and the live child weighed 4 pounds 6 ounces. By now the uterus was down to a size consistent with that of a normal puerperal organ and bleeding had nearly stopped. It was considered unsafe to proceed with any further exploration of the uterine interior although it was suspected that more molar tissue might be present. During the following three days, three large masses of tissue, not in the least resembling normal placenta, were passed. These masses were composed of material looking like bunches of machinists' cotton waste. If there had been vesicles in it, these had disintegrated and were unrecognizable as such. These fragments weighed a total of 4 ounces, which, added to the original 4 pounds 2 ounces, made a total weight of 4 pounds 6 ounces, the same weight as that of the baby.

Convalescence was uneventful except for a slight fever. The patient left the hospital on the seventh post-partum day in good condition. Repeated Friedman tests were consistently negative, as were the urinalyses. The baby developed a series of troublesome subcutaneous abscesses in various parts of the body and had a stubborn diarrhea. These setbacks were gradually overcome, and when last seen, eight months after delivery, the infant was gaining rapidly and seemed quite robust and normal.

Pathologic Report

The gross specimens were examined by Dr. I. L. Tilden who reported as follows: The placenta together with the umbilical cord weighed 4 pounds 6 ounces (2,100 Gm.). It measured 25 cm. in diameter and 6 to 10 cm. in thickness. The umbilical cord was attached eccentrically and measured 30 cm. in length and 2 cm. in diameter. The umbilical vessels on the fetal surface of the placenta were dilated and tortuous, varying in diameter from 5 to 20 mm.; they were filled with recent blood clot. One amnion and one chorion were present.

The placenta was made up of alternating masses of cystic bodies and coarse, friable, stringy, noncystic tissue. The individual cysts were generally large, some measuring 3 cm. in diameter. The intervening tissue was edematous and extremely coarse and friable. Several hemorrhagic areas were present which were even more friable. It was estimated that approximately one-half of the placenta had undergone cystic degeneration.

Microscopic examination of the cystic tissue revealed the changes associated with hydatidiform mole with, however, certain minor variations. Many of the giant villi had undergone cystic changes only in their central portions, leaving relatively thick walls (Fig. 2). The villous

stroma making up the larger portion of the cyst walls was edematous and exhibited many areas of beginning cyst formation. Most of the cysts were covered by a single layer of poorly preserved syncitial cells. Generally there was only a slight tendency toward proliferation of the trophoblastic cells although certain fields were present which did show proliferation of both syncitial and Langhans cells (Fig. 3). In certain instances the vascular supply was intact, the vessels having been pushed far toward the periphery by the central cyst formation; in most instances no vascular supply was intact, the vessels having been pushed far to-

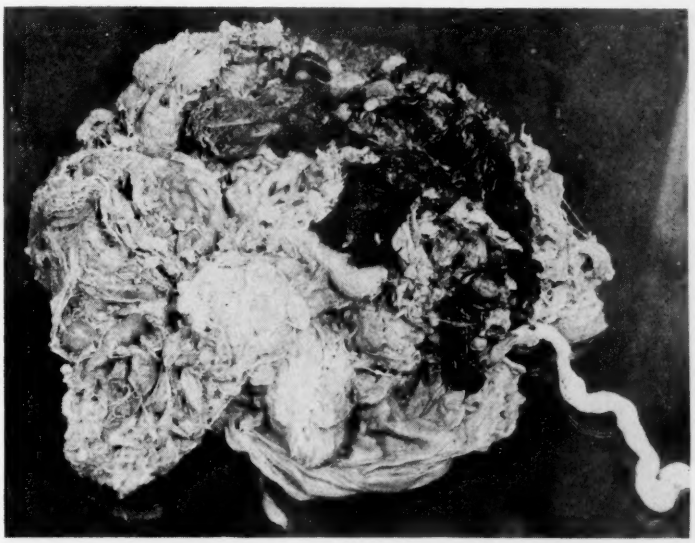

Fig. 1.—The gross appearance of the placenta after formalin fixation.

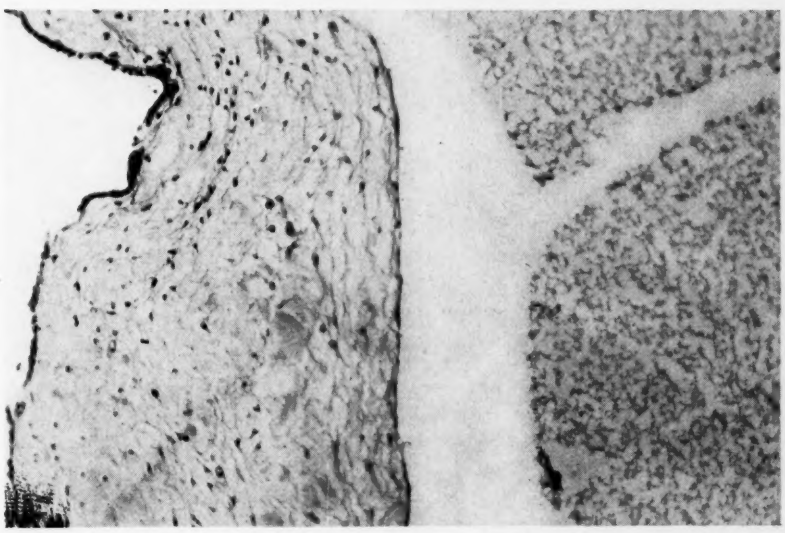

Fig. 2.—Giant villus showing relatively thick wall and central cystic change. Hematoxylin and eosin. (×130.)

ward the periphery by the central cyst formation; in most instances no vascular supply was evident.

The solid friable tissue presented a comparatively normal histologic picture. There was considerable red cell extravasation into the villous stroma but the vessels were intact and the villi were average in size and exhibited no evidence of trophoblastic proliferation.

Extensive necrosis was observed in the sections taken through the hemorrhagic tissue noted in the gross examination. This was characterized by marked red cell extravasation and leucocytic infiltration into the involved villi; actual loss of structure was observed in several areas.

The umbilical cord exhibited a normal microscopic picture.

No evidence of organization was observed in sections taken through the dilated umbilical vessels on the fetal surface of the placenta.

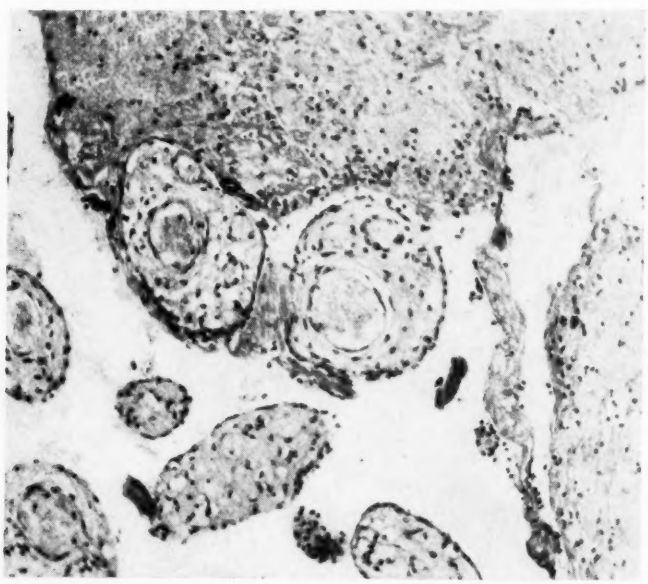

Fig. 3.—Showing necrosis characterized by leucocytic infiltration and red cell extravasation into the involved villi. Hematoxylin and eosin. (×130.)

Summary

1. The occurrence of a viable baby together in a single ovum with extensive hydatidiform mole formation is exceedingly rare.

2. The subject is reviewed herewith and such a case presented.

3. The mother in this case recovered following normal vaginal delivery, and the infant continued its normal development after a stormy beginning. Subsequent Friedman tests on the mother were negative.

4. The vesicles obtained showed the typical pathologic changes characterizing hydatidiform mole, i.e.: (1) trophoblastic proliferation, (2) hydropic degeneration of the villous stroma, and (3) scantiness of blood vessels.

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Lemmon, Wm. T., and Paschal, George W., Jr.: Continuous-Serial, Fractional, Controllable, Intermittent—Spinal Anesthesia, Surg., Gynec. & Obst. **74**: 948, 1942.

The authors present a statistical report of 1,000 patients operated upon under continuous spinal anesthesia. The point is stressed that this method is safer than the single dose technique for the following reasons:

1. Small dosage.

2. Less absorption of the anesthetic into the circulation.

3. Controllability, by withdrawal of spinal fluid. Of the one thousand cases presented, 30 were operations above the diaphragm, and in only one of these, a lobectomy, was it necessary to use supplemental inhalation anesthesia. There was little difficulty with excessive fall of blood pressure. The percentage of headaches was 2.8, which is approximately what one would expect with the single dose method. There were 34 instances of pulmonary complications. The mortality was 4.7 per cent. In no case was the anesthesia a contributing factor. The operations performed are all tabulated and represent an adequate distribution of cases. Of interest is the fact that 62 cesarean sections and 192 gynecologic operations were carried out with this technique.

L. M. Hellmann.

Department of Statistics

STUDIES OF SURGICAL MORBIDITY*

I. Abdominal Hysterectomy

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THIS is a study of surgical morbidity based on 800 abdominal hysterectomies. The inadequacies of present morbidity standards are generally recognized and the need for proper interpretation of these variations is apparent. This study includes the incidence, the factors, and the etiology of morbidity.

The 800 abdominal hysterectomies were performed in this institution between January, 1938, and July, 1942. There were 420 subtotal hysterectomies and 380 total hysterectomies. The study was made in the belief that every clinic should examine and publish its statistics from time to time for the purpose of discussion and interpretation of the facts found. By doing this, one can eliminate the prejudices, mannerisms, and false impressions which invariably develop over a period of years.

Methods and Material

The series includes both private and service, colored and white patients, operated upon by the seven attending gynecologists and residents. All of the operators used essentially the same technique, and the indications for surgery were quite uniform. Operations by the resident staff were done under the direct supervision of one of the attending gynecologists. This series of patients was studied in the same chronologic order in which the patients were operated upon, and all the abdominal hysterectomies done on the gynecologic service during this period were included.

The operations were graded as to the difficulty of procedure on the basis of 1 to 4, with a Grade 1 being the simplest procedure and a Grade 4 the most difficult type. All grading was done by one individual. The direct pathology, the associated pathology, the operating time, and all of the findings were taken into consideration in the grading of each operation.

General Morbidity

The standard used was as follows: a temperature of 100.4° F. (oral) on any two days postoperatively, excluding the first twenty-four hours, was considered morbid. This very strict standard, derived from the

*Presented at a meeting of the Chicago Gynecological Society, January 15, 1943.

obstetric morbidity standard, was used in order to classify all doubtful and borderline morbidities which are essential to a study of this kind. We well realize that this is not the ideal standard for judging morbidity as is evidenced by our findings of the causes.

Table I shows the morbidity of the entire group, and the morbidity of each of the grades in both types of operative procedure. The morbidity of the entire group was 33.87 per cent, with a morbidity of 36.57 per cent for the total hysterectomy, and 31.42 per cent for the subtotal procedure. Total hysterectomies show a slightly higher morbidity than the subtotal hysterectomies. The different grades show, as would be expected, an increase in morbidity accompanying the more difficult procedures. The Grade 4's in both groups show a morbidity of well over 60 per cent, while the Grade 1's show a morbidity below 30 per cent. With the increased trauma of the more difficult procedure, plus the more extensive pathologic involvement responsible for the Grade 4 operation, one would expect a higher morbidity.

TABLE I. RELATION OF MORBIDITY TO GRADE OF OPERATION

	NUMBER	NUMBER MORBID	PERCENTAGE MORBID
Total hysterectomy	380	139	36.57
Subtotal hysterectomy	420	132	31.42
	800	271	33.87
Total Hysterectomy			
GRADE	NUMBER	NUMBER MORBID	PERCENTAGE MORBID
1	142	40	28.87
2	150	52	41.40
3	61	30	49.18
4	27	17	62.92
	380	139	36.57
Subtotal Hysterectomy			
1	111	27	24.32
2	174	49	28.21
3	91	29	31.86
4	44	27	61.36
	420	132	31.42

TABLE II

	NUMBER	NUMBER MORBID	PERCENTAGE MORBID
Private patients	523	147	28.10
Service patients	277	124	44.78
White patients	573	162	28.27
Colored patients	227	109	48.01

TABLE III. ONSET AND DURATION OF MORBIDITY

DAY MORBIDITY BEGAN	PERCENTAGE		NUMBER OF DAYS MORBID	PERCENTAGE	
First	24.1	72.3	1	0.7	
Second	48.2		2	27.9	50.3
Third	5.0		3	22.4	
Fourth	5.0		4	13.3	
Fifth	4.6		5	12.5	

TABLE IV. MORBIDITY CAUSES

CAUSE	GRADE 1	GRADE 2	GRADE 3	GRADE 4	TOTAL	PERCENTAGE
Unknown	27	48	23	12	109	40.2
Cystitis	16	22	12	7	57	21.0
Pyelitis	3	2	4	3	12	4.4
Thrombophlebitis	2	5	1	5	13	4.7
Pulmonary embolism	5	5	1	0	11	4.0
Wound infection	5	3	2	3	13	4.7
Local infection	1	4	6	2	13	4.7
Anemia	0	2	1	1	4	4.0
Upper respiratory infection	4	4	2	1	11	2.9
Paralytic ileus	1	2	2	3	8	1.4
Dehydration and shock	1	0	0	2	3	1.1
Vaginal hemorrhage	0	1	1	0	2	0.7
Injured ureter	0	0	0	2	2	0.7
Abscess (breast, axillary, peri-anal)	1	1	1	0	3	1.1
Peritonitis	0	1	0	1	2	0.7

Table II shows the number of private and service patients with the corresponding morbidity for each, as well as the number of colored and white patients and their morbidity.

Table III shows the relation of morbidity to the number of days the patients were morbid, and the days on which they became morbid. Seventy-two per cent of the patients became morbid on the first 2 postoperative days, and 86 per cent became morbid within the first five days. Fifty per cent of the morbid patients were morbid for two or three days, and another 25 per cent were morbid for only five days.

Morbidity Causes

Table IV shows the causes of morbidity of both the total and subtotal groups in their respective grades. In order to call any one factor the cause of the morbid condition, it had to be shown by substantial confirmatory evidence to be the etiologic factor. The laboratory findings, the time of onset of the morbid condition, and the clinical picture were all taken into consideration in establishing the cause of the morbid condition, in this case the cause of the rise in temperature.

Any patient who was morbid according to the standard used, but for whom there could not be found a substantiating cause, was classified as "unknown." They were, for the most part, those patients who had a temperature above 100.4° F. for the first few days after surgery. The temperature sometimes rose as high as 102° F. and then gradually returned to normal in the next two or three days. These patients made an uneventful recovery and did not remain in the hospital any longer than the nonmorbid patients. There were patients who unquestionably had a definite pathologic etiology for their morbidity which was not detected.

Cystitis was diagnosed on the basis of daily urinalysis in the presence of both clinical symptoms and the temperature rise which characteristically appeared on the fourth or fifth postoperative day. Table IV shows that 25 per cent of all morbidities were due to either cystitis or pyelitis. When the "unknown" group is subtracted from the series, the urinary infections are found to be the etiologic factor in 43 per cent of the morbid patients. It was also noted that there were 64 patients in whom the urine was apparently "infected," but there was no rise

in temperature. The "nonmorbid" urinary infections occurred in 8 per cent of the patients with an incidence of 6.8 per cent for the total hysterectomies, and 9 per cent for the subtotal hysterectomies. Catheterized urine specimens to be called "infected" had to show more than 20 mg. of albumin and more than 10 white blood cells per high power field on two consecutive days postoperatively.

"Local infection" was an infection of the operative field, usually at the site of the cervical stump. There were 13 patients with this type of infection.

"Wound infections" were those infections of the incision which were responsible for temperature rises above the standard. That there were the same number (13) of these as there were local infections is coincidental.

There were 11 upper respiratory infections and all so classified were minor in nature.

Of the 11 patients with pulmonary embolism in the series, 10 occurred in the first two grades, i.e., the easier operative procedures. Five of these embolisms proved fatal. Eight of the 11 were in colored patients. Four embolisms occurred in the total operation, while seven occurred in the subtotal procedure. Only two of these patients with embolism had a diagnosed thrombophlebitis and both of these involved the leg. There were 13 patients with thrombophlebitis diagnosed as the etiologic cause of a morbidity.

An axillary abscess and a breast abscess followed the injection of subcutaneous fluids given in that area.

There were two patients in the series with eviscération, but only one of them became "morbid."

There were two instances in which the ureter was injured. One was in a subtotal operation and the other in a total hysterectomy, and both were Grade 4 operative procedures.

There were 3 patients in whom injury to the bowel was a morbidity factor.

Relation of Pathology to Morbidity

Table V (a and b) shows the relation of pathology to morbidity. Each operation was classified as to its predominate pathologic condition.

Under the heading "undetermined pathology" were included patients with functional bleeding, endocrine dyscrasias without demonstrable pathology, lacerations of the childbirth canal without any other pathologic condition, and patients with a pregnancy where a hysterectomy was done therapeutically and the cause for the operation was not demonstrable pathologically. It is also worth while to point out that in the group of patients classified under "undetermined pathology," the morbidity rate is very near that of the general overall morbidity average.

Classified under "tumors" were patients with benign neoplasms of either the uterus or adnexa. These operations were not complicated by any other pathologic conditions, such as adhesions from "residues," endometriosis, or previous surgery.

Classified under "previous operations" were patients who had associated pathology, usually adhesions resulting from previous abdominal surgery, but who did not have either "residues" of pelvic infection or endometriosis. Most of this group were patients with fibroids, adhesions and a history of previous surgery. Adhesions resultant from previous surgery did not increase the morbidity over the general average.

TABLE V. RELATION OF PATHOLOGY TO MORBIDITY

	GRADE 1 % MORBID	GRADE 2 % MORBID	GRADE 3 % MORBID	GRADE 4 % MORBID	AVERAGE PERCENTAGE MORBIDITY
Total Hysterectomy (a)					
Tumors	22.2	30.7	20.0	100	26.7
Residues	66.6	42.5	60.7	58.3	51.6
Endometriosis	35.2	24.3	50.0	66.6	33.8
Undetermined	36.8	--	--	--	36.8
Malignancy	15.3	70.0	100	100	51.7
Previous operation	33.3	26.6	30.0	33.3	29.4
Subtotal Hysterectomy (b)					
Tumors	23.6	22.7	39.2	66.6	25.5
Residues	25.0	32.3	37.6	59.0	36.0
Endometriosis	17.6	27.7	37.5	63.6	33.8
Undetermined	33.3	25.0	--	--	31.2
Malignancy	50.0	--	--	50.0	25.0
Previous operation	--	30.7	20.0	66.6	33.3

Under "endometriosis" were included all patients who had any endometriosis without associated malignancy, or "residues" of pelvic infection. If a patient had both a benign tumor and endometriosis, she was classified under endometriosis.

Under "residues" were included all patients who had the residues of previous pelvic inflammatory disease, either specific or nonspecific in nature. All adhesions in the pelvis, not explained by previous surgery or endometriosis, were considered to be evidence of some inflammatory process having been present. The term "residues" is one used in this series to denote the pathologic entities resulting, or residual from any previous pelvic infection, regardless of the etiology. Differentiation between specific and nonspecific types of "residues" was not made in this study. Patients with "residues" of pelvic infections had a high percentage of morbidity. In the total group it was 51 per cent.

Patients with any type of malignancy were classified under that heading, taking precedence over all other types of pathology. In the "malignant" group there were 5 patients with chorionepithelioma, and 4 patients with sarcoma of the uterus. There were 19 patients with carcinoma of the endometrium, which constituted over 50 per cent of the malignancies. There were 3 patients with carcinoma of the cervix, and 2 of these were found incidentally by the pathologist after the uterus had been removed for other causes. There were 6 patients who had carcinoma of the ovaries. In the total hysterectomy group, the malignancies show a very high morbidity rate. There were three and one-half times as many patients with malignancies operated upon in the total hysterectomy group as in the subtotal group. In Grades 3 and 4 of the total group, the morbidity is 100 per cent, and in Grade 2 it is 70 per cent.

In this series there were 32 patients who had the appendix removed. These appendices were removed either because they showed evidence of previous disease, obstruction to drainage, or there was a history of recurrent attacks. Eleven of these patients were "morbid" (34 per cent).

Mortality

There were 10 deaths in the series, giving a mortality rate of 1.25 per cent. Table VI shows the distribution of deaths in the grades and the causes. They were divided into 6 deaths in the subtotal group, and 4 deaths in the total hysterectomy group. This gives total hysterectomy a mortality rate of 1.05 per cent, and subtotal hysterectomy a mortality rate of 1.43 per cent.

TABLE VI. MORTALITY

10 Deaths, 1.25%	{5 deaths pulmonary embolism, 50% {5 deaths other causes, 50%
Total hysterectomy, 4 deaths, 1.05%	Subtotal hysterectomy, 6 deaths, 1.43%
Grade 1, 1 (peritonitis and pneumonia)	Grade 1, 1 (pulmonary embolism)
Grade 2, 1 (peritonitis and paralytic ileus)	Grade 2, 4 (3 pulmonary embolism; 1 anesthetic)
Grade 3, 1 (pulmonary embolism)	Grade 3, 0
Grade 4, 1 (peritonitis and pneumonia)	Grade 4, 1 (uremia)

Discussion

The word "morbidity" is defined by Webster's dictionary as "(1) being in a diseased or abnormal state; (2) caused by or denoting a diseased condition; (3) of or pertaining to disease; pathological." The word is derived from the Latin "morbidus" meaning "affected with or pertaining to disease." The connotation of the word when used in a study such as this has to do with those deviations from the ever elusive term "normal postoperative course."

The need for a standard of morbidity in surgical procedures is of utmost importance. The need is not to set up a standard by which individual patients can be judged morbid or nonmorbid, but rather to set up a standard by which groups of patients in studies such as this can be evaluated and compared to other such studies. There is no universally accepted standard today by which such a study can be made. The numerous and various standards in use today have, for the most part, emanated from the obstetric standard, similar to the one used in this study. Because of years of attacks on the maternal and fetal morbidities and mortalities, the obstetrician has established and agreed upon a standard. However, the surgeon's work is so varied, and there are so many factors entering into the establishment of an effective, workable standard that it has not been feasible. Emergency, traumatic, and elective surgery, as they vary in each of the surgical specialities, all contribute to the confusion. It has been suggested that a standard should be worked out for each of the more common surgical procedures; i.e., appendectomies, herniorrhaphies, mastectomies, cholecystectomies, hysterectomies, etc. The importance of such a standard is not to set up an axiomatic law under which all morbid patients will fall into "pigeonholes" of classification, but to act as an average, or "norm," for the purpose of analysis and comparison.

It is not possible for one group to establish a standard from one study such as this. The representatives of various organizations examining numerous series of patients, and studying the results of a composite group in an analytical manner, could alone set up such a standard which would be both workable and acceptable. With such a morbidity standard our efforts could then be directed toward those factors which are now responsible for the complications arising from surgery.

It has not been our purpose in this presentation to advocate either the subtotal or the total hysterectomy as a routine operative procedure. We cannot emphasize too strongly our objection to "routine" surgical operations in gynecology. Adherence to fundamental surgical and pathologic principles results in rational variation to individual problems. The experience of the operator, the pathology involved, and the difficulty of the individual operation are extremely important in judging which operation is the procedure of choice.

The grading of the individual operations was considered a most fundamental part of the study, for it is only by comparing similar types of operations in relation to their pathology and operability that a fair comparison can be made. It has been brought out (Table I) that morbidity rises with increased technical difficulty rather than being associated with either operative procedure per se.

In evaluating the literature on mortality and morbidity in hysterectomies, it is important to keep in mind which type of operation is being advocated, or is done "routinely." Smith,[1] in 1940, reported a series of 1,200 hysterectomies, using the same morbidity standard we have used here. He found a morbidity rate of 34 per cent for the entire series with a morbidity rate of 46 per cent for the total hysterectomy, and 28 per cent for the subtotal hysterectomy. His series showed a predominance of the subtotal operations. In clinics where the total operation is the one of choice, it is usually shown that the subtotal hysterectomy has a much higher mortality and moribidity rate. McDonald[2] in reporting 2,773 hysterectomies, in which 94.4 per cent were total hysterectomies, shows a mortality rate of 1.02 per cent for the total hysterectomy, and a mortality rate of 2.75 per cent for the subtotal. The reason for this is probably that in these clinics the subtotal operation is done only in those patients where the total operation is not feasible due to technical difficulties. Hence, nearly all of their subtotal operations are of Grades 3 and 4, in which the morbidity rates are much higher. The converse is often true in clinics where the subtotal hysterectomy is the procedure of choice, and the total operation is done only in those patients where there is enough cervical pathology to demand its removal. Dupertius and Zollinger,[3] in reporting 1,000 cases from a general surgical service where 73 per cent of the operations were the subtotal hysterectomy, show a mortality rate of 4 per cent for the total operation, and 1.6 per cent for the subtotal operation. Their report includes a survey of the literature in which the subtotal operation is the predominant procedure, and in 16,851 hysterectomies the mortality rate was 2.4 per cent for the subtotal operation, and 4.1 per cent for the total hysterectomy. As a result of such discrepancies, it is important to compare the difficult subtotal operations with the equally difficult total hysterectomies.

The close parallelism between the morbidity rate of the colored and service patients is to be expected (Table II). Although there were many private colored patients, the majority were service patients. The high morbidity rate found in these two groups is due to the high percentage of "residues" of tubal disease. The increased percentage of "residues" means more extensive pathologic involvement of surrounding tissues in the pelvis, and, hence, the operations were found to be in the grades which carry the high morbidity rates.

Routine appendectomies are not done on this service. We do not think that the benefit gained by the so-called "prophylactic" appendec-

tomy is warranted when surgical principles must be violated. We believe that disease found in the appendix and a history of recurrent appendicitis are the indications for its removal. We feel that our series of appendicies removed is far too small to justify any claims as to the advisibility of removing the appendix at the time of other surgical procedures in the abdomen. No statement other than our policy in this regard can be made.

In regard to the relation of pathology to the morbidity rate (Table V), it is interesting to note the even distribution of the morbid patients in the subtotal group. The patients with "residues" are the highest. One would expect the tumors without "residues," adhesions, or endometriosis to show the lowest morbidity rates, for these are the simplest types of operations from the technical standpoint. In the presence of previous pelvic infections, one would expect a higher morbidity rate due to the more difficult procedure involved, plus the fact that there may be latent deposits of bacteria which are activated by surgery. This assumption is more clearly shown in the total hysterectomy group. In the patients who had nothing more than a previous abdominal operation to complicate their picture, we find the morbidity rate near the general average. As there is presumably no previous infection factors in these patients, it would seem that the presence of previous infection and inflammatory processes are an important factor in raising morbidity.

All patients with a known or presumed malignancy were subjected to total hysterectomy. Complicated surgical procedures were necessitated by varying degrees of invasion and metastases, which accounts for the high percentage of morbidity in these groups.

In the group classified under "undetermined" pathology the morbidity rate is near the general average, which shows that even in the presence of minimal technical difficulties there is a rather high morbidity rate as measured by present standards. That is, the hysterectomy per se carries with it a certain morbidity rate, and potential mortality which cannot be dismissed. It is also interesting to note that in the patients who had endometriosis, which many times presents a most complicated technical picture, the morbidity rate was near that of the general average.

The distribution of the causes of morbidity in the grades of operations shows very little variation (Table IV). Most important is the occurrence of pulmonary embolism. Ten of the eleven in the series occurred in Grades 1 and 2. It is of interest to note that 4 of the 5 fatal instances of embolism, and 8 of the 11 in the series were in colored patients. Nearly twice as many instances of embolism occurred in the subtotal operation as in the total. All patients with pulmonary embolism were treated with intravenous papaverine, atropine, and oxygen.

The 26 patients who had local and wound infections constitute a separate group in which there was drainage and true infection. Most of these patients followed a characteristic course. The drainage began on the fifth to the tenth postoperative day and paralleled the temperature rise in amount and duration. The length of the operation, the difficulty of the procedure, the presence of infection, and the trauma to the tissues were all factors in producing these infections. They constitute 9.58 per cent of all the morbid patients.

Urinary tract infections account for 43 per cent of the identified morbidities, and 8 per cent of the patients had "infected" urine without a rise in temperature. This institution has always been conscious of the importance of "residual" urine, and all of the patients were on

a catheterization routine with this factor uppermost in mind. The etiologic factors of these urinary infections and possible theories as to their elimination is the subject of a subsequent report.

The "unknown" morbidities form an interesting group which demands considerable discussion. It was found that this group followed a definite temperature pattern in most instances. The temperature rises in this group are thought to be within the physiologic expectancy, and consequently are not true morbidities. The fact that these patients made an uneventful recovery, and did not have any positive laboratory findings seems to show that these patients did not have actual pathologic morbid conditions. We have thought that the term "physiologic morbidity," or "physiologic reaction," as compared to "pathologic morbidity" would be a better way to distinguish them. However, there were in this group a certain number of pathologic conditions of unknown etiologies.

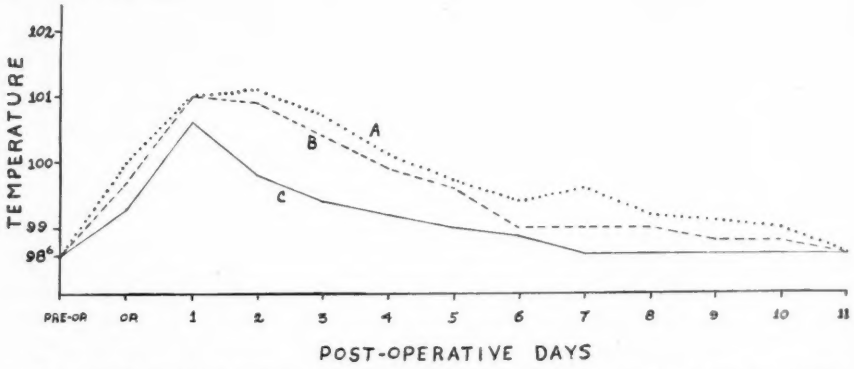

Fig. 1.—This shows a composite temperature curve of (*A*) 50 total hysterectomies, and (*B*) 50 subtotal hysterectomies from the "unknown" morbidity group. These patients are considered "physiologic" morbidities. Curve (*C*) shows 50 total and subtotal hysterectomies which were nonmorbid according to the standard used in this presentation.

Fig. 1 shows a composite temperature curve of 50 total hysterectomies and 50 subtotal hysterectomies that were in the "unknown," or "physiologic," morbid class. The lower curve shows a composite temperature curve of 50 nonmorbid total and subtotal hysterectomies. This latter group is nonmorbid by our present standard. We do not believe that the temperatures represented by the two upper curves are true morbidities. Table IV shows that 72 per cent of the patients became morbid on the first two days after surgery, and that 50 per cent of the patients were morbid for two or three days according to the standard used here. This further substantiates and augments the belief that these are not pathologic temperature curves. We do not feel that every patient with a temperature curve that falls above this average is morbid, but we do feel that in a study of a large series of operations the temperature curves that fall above this composite will be pathologic in nearly every instance, and an etiologic factor can be found for the morbid condition. Again let us state that the need for a morbidity standard is not only to judge the individual patient's postoperative course, but to study large groups; to analyze and to compare.

An intensive search of the literature has failed to produce a standard for surgical morbidity that has been accepted by any major surgical organization. Beck,[4] in 1939, urged that the surgical societies establish

a morbidity standard as the obstetricians have done. Hunt[5] urged repeatedly for careful analysis of surgical complications and deaths, but not for an actual morbidity standard.

We feel that to make such a standard workable, studies similar to this one should be undertaken for each of the more common surgical procedures, and in this way differentiate between "pathologic" and "physiologic" conditions. These would vary greatly in different operations.

Summary and Conclusions

1. An analysis of 800 abdominal hysterectomies is presented, and the incidence, factors, and etiology of morbidity involved are discussed.

2. The morbidity rate for the total hysterectomy was slightly higher than that for the subtotal operation, while the mortality rates for each procedure were approximately the same in this study.

3. Difficult technical procedures increased morbidity.

4. "Residues" of pelvic infection increased morbidity.

5. Urinary tract infections caused 43 per cent of the identified morbidities.

6. A differentiation between "physiologic" and "pathologic" morbidity must be made when temperature and time are used as a standard for morbid conditions.

7. A composite temperature curve of 150 hysterectomies is offered as a guide for differentiating the "physiologic" from the "pathologic" temperature rises following surgery.

8. Since there are no standards for surgical morbidity which are adequate for present-day needs, they should be established for each of the more common surgical procedures.

References

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2. McDonald, E. P.: New York State J. Med. **39**: 503, 1939.
3. Dupertius, S. M., and Zollinger, R.: Surg., Gynec. & Obst. **67**: 689, 1938.
4. Beck, W. C.: Arch. Surg. **39**: 478, 1939.
5. Hunt, E. L.: New England J. Med. **203**: 616, 1930.

Society Transactions

NEW YORK OBSTETRICAL SOCIETY

MEETING OF JANUARY 12, 1943

The following case report and paper were presented:

Case Report: An Anomaly of the Sacrum Complicating Pregnancy. Dr. Hervey C. Williamson.

A Further Contribution to the Syndrome of Fibroma of the Ovary With Fluid in the Abdomen and Chest, Meigs' Syndrome. Dr. Joe Vincent Meigs of Boston (by invitation). (For original article, see page 19.)

MEETING OF FEBRUARY 9, 1943

The following case report and paper were presented:

Case Report: Accessory Hypoplastic Kidney and Ureter, Clinical Study and Operation. George F. Hoch, M.D. (by invitation), and William T. Kennedy, M.D.

Paper: Eclamptic Toxemia With Special Reference to Etiology. Herman W. Johnson, M.D., Houston, Texas (by invitation).

OBSTETRICAL SOCIETY OF PHILADELPHIA

MEETING OF NOVEMBER 5, 1942

The following papers were presented:

Acute Intestinal Obstruction Due to Bands Complicating Pregnancy. Frank B. Block, M.D., and Phoenix M. Sales, M.D. (For original article, see page 134.)

The Importance of Focal Infection in Obstetrics. Myer Solis-Cohen, M.D. (by invitation).

An Attempt to Correlate the Pre-Eclamptic State With a Congenital Anomaly of the Kidney. Robert M. Hunter, M.D.

MEETING OF DECEMBER 3, 1942

The following paper was presented:

Favorable Response of Advanced Endometriosis to Testosterone Propionate Therapy. John C. Hirst, M.D. (For original paper, see page 97.)

MEETING OF JANUARY 7, 1943

The following papers were presented:

Two Cases of Congenital Anomalies of the Gastrointestinal Tract, with Autopsy Findings. Paul Morris, M.D., (by invitation).

Early Pseudomyxoma Peritonei in a Case of Fetal Meconium Peritonitis. Raphael Lattes, M.D., (by invitation). (For original article, see page 149.)

Hypothyroidism as a Problem in Women, Second Report. Carl Henry Davis, M.D. (For original article, see page 85.)

The Simpson Operation in the Treatment of Uterine Retroflexion. John B. Montgomery, M.D.

CHICAGO GYNECOLOGICAL SOCIETY

MEETING OF DECEMBER 18, 1942

The following paper was presented:

Early Stages in Human Development With Special Reference to the Pre-Villous Ovum. Arthur T. Hertig, M.D., Boston, Mass. (by invitation). To be published in a later issue.

MEETING OF JANUARY 15, 1943

The following papers were presented:

The Effect of Complementing the Diet in Pregnancy With Calcium Phosphorus, Iron, and Vitamins A and D. Fred L. Adair, M.D., William J. Dieckmann, M.D., and (by invitation) Herbert Michel, M.D., Florence Dunkle, M.S., Sylvia Kramer, Ph.D., and Edna Lorang, B.S. (For original paper, see page 116.)

Studies of Surgical Morbidity: I. Abdominal Hysterectomy. Harold O. Jones, M.D., and (by invitation), Leo W. Doyle, Jr., M.D.

Department of Reviews and Abstracts

Selected Abstracts

Abortion

Caffaratto, T. M.: A Rare Case of Massive Decidual Expulsion Following a Five Months' Abortion, Ginecologia **6**: 229, 1940.

The author describes a case of massive decidual expulsion following an abortion in the fifth month of pregnancy. He demonstrates, in 9 photomicrographs, a moderate inflammatory change in the decidual tissue. The accompanying of a placenta marginalis, similarly involved, suggests to the author that inflammation of a low-implanted placenta may well explain the etiology of this massive decidual expulsion.

CLAIR E. FOLSOME

Dunn, Halbert L.: Frequency of Abortion, Its Effects on Maternal Mortality Rates, Vital Statistics, Dept. of Commerce, Bureau of the Census, Special Reports **15**: 431, 1942.

Dr. Dunn, in this paper presented at the Conference on Abortion Problems, sponsored by the National Committee on Maternal Health, in June, 1942, at New York City, states that the frequency of abortion, as it effects maternal mortality rates cannot be determined without a very intensive, as well as extensive, study which does not appear feasible at this time. However, rough approximates indicate that about 50 per cent of the deaths from abortions are tabulated in the mortality statistics as such.

The number of deaths from abortions, in the United States in 1940, has been estimated to be between 3,000 and 4,000 in number. This figure constitutes about 30 to 35 per cent of maternal deaths from all causes. The general rates for causes of maternal death has been decreasing but the death rate from abortions has probably remained unchanged.

By using three arbitrary constants: (1) of 1 abortion to every 5.6 confinements for the urban areas; (2) of 1 abortion to every 9.4 confinements for the rural areas; and (3) assuming the fatality rate from abortion to be 1 per cent, it is possible to calculate the number of abortions and abortion fatalities. The estimated number of annual urban abortions was 188,393; rural abortions, 143,936 with a total of 332,393 per year, in this country. The annual fatalities from abortion can be estimated as about 3,300 in number.

One common source of error in mortality statistics on abortion is due to the confusion regarding the definition of the term "abortion" among the States, whether lunar or of calendar month basis, whether a five or seven months' time period differentiates abortion from "age of viability," "stillbirth," and premature death. The reporting habits of the physicians constitute another common source of error.

Dr. Dunn's article contains 5 excellent reference tables and 3 valuable charts which go far to crystallize the multiple complexities of statistics on the abortion problem. Copies of this article can be obtained from the Bureau of the Census, Washington, D. C.

CLAIR E. FOLSOME

Rutherford, Robert N., and Mezer, Jacob: Regeneration of Uterine Mucosa After Spontaneous Abortion and Normal Delivery, J. A. M. A. **119:** 124, 1942.

Twenty-five cases were included in this study. The program of regeneration follows that laid down by Williams in his monograph on this subject. The authors showed that patients who are lactating regenerate the endometrium at approximately the same rate as the nonlactating patients. However, if ovulation is inhibited as by continued lactation, the endometrium tends to remain as resting or mildly proliferating endometrium, until at last the previous ovarian rhythmicity breaks through.

A similar process was repeated in cases of spontaneous abortion. It was found that the endometrium regenerates more rapidly and menstruation ensues quicker in cases where thorough curettage follows the abortion. Routine curettage is therefore recommended in cases of spontaneous abortion, even though all products of conception have been identified as extruded. Patients may be urged to seek impregnation within two weeks after spontaneous abortion. Following a normal full-term pregnancy, the patient is susceptible to impregnation after six weeks, although lactation may inhibit ovulation for a longer period of time.

WILLIAM BERMAN

Leon, Juan: Simultaneous Therapeutic Abortion and Sterilization (Value of Surgical Methods by the Vaginal Route), Arch. de la clin. obst. y ginec. **1:** 113, 1942.

Leon presents the conclusions of a longer paper which appeared in *La Prensa Medica Argentina* in 1941. The question whether sterilization should be performed simultaneously with abortion or delivery frequently arises. Many obstetricians do a salpingotomy along with curettage while others prefer to wait several days or even weeks after the abortion. The same problem arises in connection with delivery at term. Some (Ottow and Anselmino) advise Menge's operation within twenty-four hours of delivery to avoid a second hospitalization and because the wounds heal better during the involution period. Eymer advises delay until the third or fourth day, while Engelman believes that dangers of infection are greater during this period and prefers to wait six weeks. With this procedure the patient may become pregnant again. However, in such cases curettage may be done a few days after sterilization if the Friedman test is positive. Perhaps the best way is to keep the patient in the hospital for the six weeks' period, although the attendant expense and the long absence of the woman from her home are definite drawbacks.

The author concludes that at the present time there are not many indications for vaginal surgery in simultaneous abortion and sterilization. The need for vaginal surgery has been reduced for several reasons: speed is not considered as essential as safety; in the first two months of pregnancy there is no necessity for supplanting the current obstetrical practices of dilating the cervix and curettage; tubal sterilization by colpotomy is more dangerous during pregnancy than later; x-rays, radium and other biologic methods of sterilization are available.

The need for vaginal surgery occurs principally in the third month of pregnancy when uterine evacuation by obstetric methods is difficult and dangerous because of the size of the pregnancy and because simple rupture of the amniotic sac is not practicable.

There are four techniques for vaginal "minor" cesarean sections: vaginocervical-lower uterine segment, vaginolower uterine segment with longitudinal incision, vaginolower uterine segment with transverse or arciform incision, and vaginocorpus. The last three are generally preferred since the cervix is not involved. These different types of hysterotomies can be combined in the same operation with any of the methods of tubal sterilization, permanent or temporary.

If the least operative trauma is desired in a patient in poor condition, and especially if the pregnancy is a little advanced, sterilization should be deferred. If the cervix is infected, opening the peritoneal cavity to perform a sterilization constitutes a definite and serious danger. In such circumstances, if a surgical method is necessary, cesarean section by the vaginocervicolower uterine segment or vaginolower uterine segment routes is preferable, the latter especially when cervicitis is present, leaving until later sterilization by colpotomy or other surgical (Menge, Stoeckel) radiation or biologic methods. Abdominal hysterotomy may be combined with sterilization.

J. P. GREENHILL

Wenner, R.: The Significance of a Successfully Overcome Threatened Abortion on the Subsequent Course of Labor, Monatschr. f. Geb. u. Gynäk. **112:** 325, 1941.

A review of the literature reveals that if pregnancy continued after threatened abortion there was a decided increase in premature deliveries and complications during labor. Furthermore, more deformed babies were born and many of the babies later proved to be inferior intellectually and physically. The author investigated 92 cases of threatened abortion where the abortion was prevented. Premature labor occurred in this series in 23.9 per cent as opposed to the usual incidence of 16.2 per cent. Only one deformed baby was delivered in his series. Operative deliveries were necessitated twice as frequently as usual. Complications on the part of the placenta were greatly increased. The author concludes that with the present form of therapy, abortion may be prevented and healthy babies obtained.

J. P. GREENHILL

Benthin, W.: Prognosis and Possibilities of Modern Therapy of Febrile Abortion. Geburtsh. u. Frauenh. **2:** 393, 1940.

According to W. Benthin, complications are to be anticipated in approximately 15 per cent of febrile abortions. The mortality rate is 7 per cent, much higher than in febrile puerperal states. Of patients with parauterine infections at the time of hospitalization, 31 per cent die. A considerable number remain sterile, and those with primary recovery may develop later sequelae. Expectant treatment offers best results in cases in which infection is confined to the uterus. Spontaneous expulsion takes place under expectant treatment in from one-sixth to one-third of the cases. Quinine and ergotamine tartrate promote the expulsive efforts, especially if used with vaginal tamponade. This tamponade stimulates uterine contractions and prevents excessive loss of blood. The use of carbon dioxide applied within the uterus and of the ice bag are valuable in restricting the infectious process to the uterine cavity. Early medication with sulfanilamide is advisable for prevention and arrest of general septic infections and in peritonitis. The expectant treatment requires strict rest in bed. A well-planned expectant treatment prevents sepsis and pyemia and parauterine infections. Operative evacuation of the uterus can be tried without much danger five days after the fever has subsided. An earlier or immediate surgical evacuation is permissible only in extremely urgent cases. There exists no vital indication for operative evacuation as long as the cervical canal is still closed. This should be kept in mind, especially in the presence of parametritis, peritonitis and inflammations of the adnexa. If the cervical canal is open and if severe hemorrhage exists, intervention is permissible, and if placental parts are already undergoing expulsion, their removal is indicated. The digital method is the most reliable and least harmful. It should be performed with deep anesthesia and as carefully as possible. Introduction of carbon into the evacuated uterus promotes detoxication and rapid discharge of secretions. Azosulfamide, dextrose, continuous infusions, administration of vitamins, and blood transfusion are the most important aids in the treatment of infection. All febrile abortions should be treated in a hospital.

J. P. GREENHILL

Uttley, K. H.: After-Histories of the Pregnancies of Over 3,000 Chinese Multigravidae in Hong Kong, Chinese M. J. **59**: 543, 1941.

A statistical investigation has been made into the histories of 3,134 consecutive Cantonese multigravidas attending an antenatal clinic in Hong Kong. All such patients were questioned as to what had happened to their previous pregnancies, how the pregnancies had terminated, and what had happened to the children subsequent to delivery and up to the time of this investigation. The results are tabulated for each group of gravidas. The finding was that no matter what group of gravidas one dealt with, the miscarriage rate was approximately 7 to 12 per cent, the infantile and childhood death rate (including stillbirths) was 30 to 35 per cent, and the percentage living was 58 to 65 per cent.

C. O. MALAND

Dietel, H.: Technic of Removal of Uterine Mole, Zentralbl. f. Gynäk. **64**: 1050, 1940.

Dietel discusses the risks of infection and perforation in the usual methods of removal of uterine mole as well as the danger of leaving fragments behind. He uses a special blunt curette, 36 cm. long with a loop of 35 mm. width, 8 mm. high. In order to thicken the uterine wall, posterior pituitary extract is given intravenously just before beginning curettement and a hand is kept over the fundus to help maintain contraction. As a diagnostic aid Dietel points to the very rapid sedimentation of the blood in the first hour alone. In his series of 10 cases sedimentation in the first hour was from 8 to 78 mm. with an average of 40 mm.

R. J. WEISSMAN

Schultze, K. W.: Fetal Congenital Abnormalities, Their Cause and Clinical Significance, Ztschr. f. Geburtsh. u. Gynäk. **121**: 242, 1940.

The literature dealing with germ plasm deficiency as a cause of abortion is discussed at length and an estimation made of its application to the practical social problem of abortion in Germany. Philipp is quoted as estimating that for the 1.3 million births per year in "Old Germany" (Altreich) there are 220,000 abortions. The various nonhereditary disturbances in the mother are discussed with special stress laid upon corpus luteum deficiency. Various statistical expressions (His, Mall, etc.) are presented and a final estimate made that one abortion due to germ plasm deficiency may be expected for every 13 live births. This alone would account for 100,000 of the estimated number of abortions.

The author states that criminal abortions have decreased by 80 per cent in the Altreich in recent years. He also estimates that abortions due to treatable causes were decreasing in a group of European countries before the present war. This gradually increased the proportion of abortions due to germ plasm deficiency, and references are given to studies which have supported this. Since many of the hereditary lethal combinations which cause abortion are sex linked and the vast majority of such abortions which occur in the first four months of pregnancy affect male fetuses (Fig. 4, p. 260), an increase in the percentage of males aborted will indicate a decrease in other causes of abortion than germ plasm deficiency. This apparently was occurring before the war.

A plea is made for more careful and complete examination of abortion material in order that more accurate information may be obtained.

An excellent bibliography is attached.

J. L. MCKELVEY

Winkler, H.: The Active Treatment of Febrile Abortion, Also a Contribution to the Question of Secondary Sterility, München. med. Wchnschr. **87**: 1052, 1940.

Dr. Winkler states that there is today no uniform treatment of "septic uncomplicated abortion" (fever but no inflammatory changes of the para- and perimetrium or of the pelveoperitoneum). He favors the active treatment and gives a statistical study of 158 cases of febrile abortions treated from July, 1933, to July, 1940. One hundred and thirty-eight were treated radically (4 deaths), 7 conservatively (1 death), and 13 by a combination of both (no deaths). In competent hands he claims that the active treatment of febrile abortions, by disinfecting the uterine cavity with an Iodine solution, has three advantages: (1) lowered mortality, (2) shorter stay in the hospital and a quicker convalescence, (3) and only a small percentage of the patients become sterile.

C. E. Proshek.

Vogt-Møller, P.: The Therapeutic Application of Vitamin E in Human Abortions, Acta. obst. & gynec. Scandinav. **20**: 85, 1940.

A survey of the therapeutic application of vitamin E is made by Vogt-Møller who found that vitamin E has proved to be most valuable in the treatment of habitual abortion. In a series of cases this vitamin successfully prevented abortion in from 75 to 80 per cent of the cases. Likewise, vitamin E has been successful in cases of threatened abortion, premature separation of the placenta, and toxemias of pregnancy. On the other hand, this vitamin has proved useless in cases of primary and secondary sterility, amenorrhea, dysmenorrhea, menorrhagia, and genital hypoplasia and the menopause.

In some cases of irregular glandular hyperplasia, vitamin E has yielded favorable results.

The author points out the relationship between vitamin E and the sex hormones, particularly progestin. He also emphasizes the possible beneficial effect of vitamin E in the treatment of some neurologic disorders.

J. P. Greenhill.

Collins, Conrad G., Weed, John C., and Collins, Jason H.: The Treatment of Spontaneous, Threatened, or Habitual Abortion, Surg., Gynec. & Obst. **70**: 783, 1940.

Wheat germ oil therapy forms a valuable basis for the treatment of spontaneous and/or habitual abortion.

Wheat germ oil therapy should be fortified by the administration of progestin and/or thyroid extract when necessary.

The fear of delivering a malformed fetus in cases in which spontaneous or habitual abortion has been successfully combatted is over-emphasized.

All efforts should be made to control spontaneous abortion or habitual abortion by the use of all known remedies which have been proved of value.

The results in 36 patients so treated were presented to substantiate these views.

William C. Henske.

Anwandter, K.: Metrorrhagia Probably Due to Avitaminosis, Bol. Soc. chilena de obst. y ginec. **5**: 3, 1939.

The author reports the similar cases of two women aged 28 and 25 years, respectively, both with postabortive bleeding due to retained decidua after light curettage. A few days after the second curettage each patient had profuse metrorrhagia. Calcium chloride, auto-hemotherapy, vasoconstrictors, and other

therapy was tried without success. Hemorrhage in each case ceased shortly after an injection of vitamin C. In the discussion, the lack of controlled studies to establish the fact of a hypovitaminosis was pointed out. It was also claimed that vitamin C was effective in controlling melena neonatorum.

R. J. WEISSMAN.

Jeffcoate, T. N. A.: Missed Abortion and Missed Labour, Lancet **238**: 1045, 1940.

Intrauterine death of the products of conception is followed by a decrease in the amount of estrogen in the blood stream. Administration of estrogens to patients with missed abortion and missed labor so increases the sensitivity of the uterus that its evacuation is usually promoted. The method of induction described here was successful in 48 out of 55 consecutive cases. Expulsion of the products of conception was free from complications, such as uterine hemorrhage and infection.

Fourteen cases were treated with estrone or estrone benzoate, 30 with extradiol bonzoate, and 11 with stilbestrol. The following technique is suggested: Estradiol benzoate is given intramuscularly in a dose of 2 mg. every eight hours for seven or eight days. If abortion has not taken place by the fifth day, 10 gr. of quinine hydrochloride are given each hour for three doses and followed by four injections of 0.5 c.c. of posterior pituitary extract at intervals of an hour. This treatment is repeated on the eighth day if the products of conception still remain in the uterus. When stilbestrol is used instead of estradiol benzoate, 2 mg. are given by mouth thrice daily, or 1 mg. every four hours, for seven or eight days. The quinine and pituitary extract are also given when required on the fifth and eighth days.

Induction of labor was successful in 28 of 29 patients beyond twenty-eight weeks of pregnancy, and in only 9 cases were accessory uterine stimulants necessary. It was successful in 20 to 26 cases before twenty-eight weeks, but quinine and/or pituitary extract was used in 11.

CARL P. HUBER.

Opazo, Victor: Postabortive Metastatic Panophthalmitis, Bol. Soc. chilena de obst. y ginec. **4**: 199, 1939.

A 40-year-old multipara, 3-months pregnant, took quinine and aborted. Severe hemorrhage followed and a curettage was performed. The following day she presented general signs of infection, and that same afternoon she suddenly lost her vision. On examination the right eye appeared swollen but was painless. The vitreous soon became purulent. There was intense edema of the upper eyelid.

Treatment consisted of sulfanilamide, uterine tonics, and vaginal douches. The eye was enucleated with subsequent recovery of the patient. No mention is made of recovery of vision in the opposite eye. Discussing various theories of the etiology of the ophthalmitis, the author concludes that the most important thing is the differentiation from gonococcal conjunctivitis. Absence of the Neisserian organism, absence of purulent conjunctivitis and pus in the anterior chamber or vitreous along with protrusion of the globe and limitation of its mobility are the essential diagnostic points.

R. J. WEISSMANN.

Yero Bou, E., and De La Vega, A. M.: Treatment of Septic Abortion, Rev. cubana de obst. y ginec. **1**: 117, 1939.

The authors reviewed 415 cases of incomplete abortion on their service. Curettage was practiced in 285 cases; 34 did not go on to complete abortion and medical treatment alone was given the remaining 96 cases. Of those curetted, 42.5 per cent were febrile on admission. Comparing immediate to deferred curettage, the authors found no complications if the operation was done on an afebrile patient.

In a special ward 37 infected cases were studied. Twenty-two improved without intervention. Sulfanilamide, ergotamine tartrate and general supportive measures were employed. Of the remainder, 2 had immediate curettage for acute hemorrhage and 13 were curetted after an average of 3 afebrile days. All patients in this group of 37 confessed to chills and high fever at home and many had been criminally aborted. The average stay in the hospital was eight days.

R. J. WEISSMAN.

Ortiz, N. C.: Considerations in the Treatment of Uterine Perforation, Rev. méd. latino-am. **25**: 276, 1939.

The percentage of surgical perforations varies from 0.5 per cent to 1.5 per cent. In the author's clinic, over 500 curettages were performed, with 4 perforations. Four case histories are given, one of a fatal case involving several intestinal perforations. Ortiz feels that expectant treatment should be followed in simple perforation in the absence of signs of infection or lesions of the other viscera. All others should be subjected to laparotomy, reserving the vaginal approach for exceptional cases. Intestinal lesions should be carefully searched, even though the patient does not appear to be toxic. Whenever possible the uterus is sutured and ovaries are preserved. The fundus is amputated if necessary. Gangrene of the uterus is the author's only indication for total or subtotal hysterectomy in this condition.

R. J. WEISSMAN.

CORRESPONDENCE

To the Editor:

In the January issue of the AMERICAN JOURNAL OF OBSTETRICS AND GYNECOLOGY, there is an article by Drs. Milton Goodfriend and Mark Daniel on the Kapeller-Adler test in the diagnosis of pregnancy. They state that the American literature in the past decade contains little reference to this test.

I wish to call attention to the fact that the writer together with Dr. I. B. Oldham, Jr., and Mr. T. J. Dunn published an article in the *Oklahoma State Medical Journal,* Volume 30, Number 6, June, 1937, relative to this test.

We reported a series of 215 cases, some of which were checked with the Friedman test. We arrived at the following conclusion: The specimen should have a specific gravity of at least 1.020 but heavier concentration is better. Either the test is positive or negative; there is no middle ground. There should be some definite standard of determination of positive and negative results similar to a Sahli colorimeter. The test in our hands has proved to be a fairly accurate one; it is easily and rapidly done. However we do not feel that this test can replace the Aschheim-Zondek or the Friedman modification.

We have continued to use this test since the publication of the above-mentioned article with approximately the same result as to accuracy.

CHARLES ED. WHITE, M.D.

March 6, 1943
Muskogee, Okla.

Necrology

ARTHUR WALTER BINGHAM, obstetrician, gynecologist, and civic leader, died at his home in East Orange, New Jersey on May 19, 1943, at the age of 71. Organized and directed the obstetric department of the Orange Memorial Hospital, was past president of the Academy of Medicine of Northern New Jersey, long known for his outstanding activities in maternal welfare work in his state. He graduated from Cornell University in 1893 and from the College of Physicians and Surgeons of Columbia University in 1896.

JAMES EWING, one of the world's foremost authorities on cancer and a pioneer in radium treatment of that disease, died in New York City, May 16, 1943, at the age of 76. He was professor of oncology at the Cornell Medical College, and consulting pathologist to various hospitals. He devoted much time to research on cancer treatment and to the development of the Memorial Hospital in New York, of which he also served as director for many years. Author, teacher, scientist, traveller, he was the recipient of many honorary degrees. Among his earlier contributions to the literature were observations and studies on eclampsia, especially the effects on the liver. Dr. Ewing was a graduate of Amherst College in 1888 and of the College of Physicians and Surgeons of Columbia University in 1891.

Item

American Board of Obstetrics and Gynecology, Inc.

The annual meeting of the Board was held at Pittsburgh, Pennsylvania, from May 20 to May 25, 1943, at which time one hundred and eight candidates were certified.

A number of changes in Board regulations and requirements were put into effect. Several of these changes are designed to broaden the requirements for candidates in Service. Examples are the allowance of a stipulated amount of credit toward special training requirements for men in Service and assigned to general surgical positions, special training allowances on a preceptorship basis for men assigned to obstetric or gynecologic duties in military hospitals and working under the supervision of Diplomates or recognized obstetrician-gynecologists, as well as credit toward the "time in practice" requirement of the Board to be allowed for time in Military Service.

The Board will no longer require a general rotating internship, but will now accept a one-year intern service, although the rotating internship is preferable. Such services must be in institutions approved by the Council on Medical Educa-

tion and Hospitals of the A. M. A. Lists of such institutions are published regularly in the Educational Number of *The Journal of the A. M. A.*

The privilege of reopening applications by candidates who have been declared ineligible has been extended to two years from date of filing the application, instead of one year.

The Board has ruled temporarily to excuse men in Military Service from the submission of case records at the stipulated examination times, thereby permitting them to proceed without further delay with the Board examinations. This does not obligate the Board, however, to waive the case record requirement for such candidates. Plans have been made to provide similarly for Service men upon their eventual discharge from the Armed Forces, and to permit the greater use of operations done while in residency or in civilian practice before the War.

The next Part I examination of the Board (written paper and submission of case records) will be held on Saturday afternoon, February 12, 1944, at a place convenient to the location of the candidate, whether he be in civilian or military life. Applications must be in the Office of the Secretary by November 15, 1943, ninety days in advance of the examination date. The time and place of the Spring 1944 (Part II) examination will be announced later.

Prospective applicants or candidates in Military Service are urged to obtain from the Office of the Secretary, a copy of the "Record of Professional Assignments for Prospective Applicants for Certification by Specialty Boards" which will be supplied upon request. This record was compiled by the Advisory Board for Medical Specialties and is approved by the offices of the Surgeons-General, having been recommended to the Services in a circular letter, No. 76, from the War Department Army Service Forces, and referred to as the Medical Officers Service Record. These will enable prospective applicants and candidates to keep an accurate record of work done while in Military Service and should be submitted with the candidate's application, so that the Credentials Committee may have this information available in reviewing the application.

Applications and BULLETINS of detailed information regarding the Board requirements will be sent upon request to the Secretary's Office, 1015 Highland Building, Pittsburgh, Pennsylvania.

Examinations

Applications for the 1944 examinations of the Board are being received at the office of the Secretary, Dr. Paul Titus, 1015 Highland Building, Pittsburgh, Pennsylvania. Booklets of information regarding Board requirements and examinations, together with application forms, will be sent upon request.

All applications for the year 1944 must be in the Secretary's Office not later than November 15, 1943, ninety days in advance of the Part I examination date.

Candidates are required to take both the Part I and Part II examinations. The Part I examination consists of the written paper and the submission of twenty-five case history abstracts, and will be conducted on Saturday, February 12, 1944. This examination will be arranged so that the candidate may take it at or near his place of residence. Upon the successful completion of the Part I examination, candidates are eligible for the Part II examination consisting of a pathology and an oral examination. This is given at the annual meeting of the Board once each year, the time and place of which will be announced later.

The Office of the Surgeon-General (U. S. Army) has issued instructions that men in Service, eligible for Board examinations, be encouraged to apply and that they request orders to "detached duty" for the purpose of taking the examinations whenever possible.

PAUL TITUS, M.D.
Secretary.

ROSTER OF AMERICAN OBSTETRICAL AND GYNECOLOGICAL SOCIETIES*

(Appears in January, April, July, October)

American Gynecological Society. *President,* George W. Kosmak, New York, N. Y. *Secretary,* H. C. Taylor, Jr., 830 Park Ave., New York, N. Y. Annual meeting cancelled.

American Association of Obstetricians, Gynecologists and Abdominal Surgeons. *President,* W. R. Cooke, Galveston, Texas. *Secretary,* James R. Bloss, 418 11th Street, Huntington, W. Va. Annual meeting, September, 1943, Hot Springs, Va.

Central Association of Obstetricians and Gynecologists. *President,* John H. Moore, Grand Forks, N. D. *Secretary-Treasurer,* W. F. Mengert, Iowa City, Iowa. Annual meeting cancelled.

South Atlantic Association of Obstetricians and Gynecologists. *President,* Oren Moore, Charlotte, N. C. *Secretary,* T. J. Williams, University, Va. Annual meeting cancelled.

A. M. A. Section on Obstetrics and Gynecology. *Chairman,* L. E. Phaneuf. *Secretary,* Philip F. Williams, 2206 Locust St., Philadelphia, Pa. Annual meeting cancelled.

New York Obstetrical Society. *President,* W. T. Kennedy. *Secretary, R. G.* Douglas, 530 East 70th St., New York City. Second Tuesday, from October to May, Yale Club.

Obstetrical Society of Philadelphia. *President,* Catharine Macfarlane. *Secretary,* James P. Lewis, 3815 Chestnut St., Philadelphia, Pa. First Thursday, from October to May.

Chicago Gynecological Society. *President,* Edward Allen. *Secretary,* Eugene A. Edwards, 104 S. Michigan Ave., Chicago, Ill. Third Friday, from October to June, Hotel Knickerbocker.

Brooklyn Gynecological Society. *President,* Samuel Lubin. *Secretary,* John J. Madden, 362 Washington, Ave., Brooklyn N. Y. First Friday, from October to May, Kings County Medical Society, 1313 Bedford Avenue, Brooklyn, N. Y.

Baltimore Obstetrical and Gynecological Society. *President,* Lawrence Warton. *Secretary-Treasurer,* John W. Haws, 9 East Chase St., Baltimore, Md. Meets quarterly at Maryland Chirurgical Faculty Building.

Cincinnati Obstetrical Society. *President,* Edward Friedman. *Secretary,* Carroll J. Fairo, Cincinnati, Ohio. Third Thursday of each month.

Louisville Obstetrical and Gynecological Society. *President,* Layman A. Gray. *Secretary,* E. P. Solomon, Hegburn Building, Louisville, Ky. Fourth Monday, from September to May, Brown Hotel.

Portland Society of Obstetrics and Gynecology. *President,* Howard Stearns. *Secretary,* William M. Wilson, 545 Medical Arts Bldg., Portland, Ore. Last Wednesday of each month.

Pittsburgh Obstetrical and Gynecological Society. *President,* J. L. Gilmore. *Secretary,* Joseph A. Hepp, 121 University Place, Pittsburgh, Pa. First Monday of October, December, February, April, and June.

Obstetrical Society of Boston. *President,* Thos. Almy, Fall River, Mass. *Secretary,* Paul A. Younge, 101 Bay State Road, Boston, Mass. Third Tuesday, October to April, Harvard Club.

New England Obstetrical and Gynecological Society. *President,* Frank A. Pemberton. *Secretary,* A. F. G. Egelow, 31 Maple Street, Springfield, Mass. Meetings held in May and December.

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*Changes, omissions, and corrections should be addressed to the Editor of the JOURNAL.

Pacific Coast Obstetrical and Gynecological Society. *President,* T. Floyd Bell. *Secretary-Treasurer,* William Benbow Thompson, 6253 Hollywood Boulevard, Los Angeles, Calif. Next meeting undecided, probably San Francisco, Calif., November 5-6, 1943.

Washington Gynecological Society. *President,* John Warner. *Secretary,* L. L. Cockerille, 900 17th Street, N. W., Washington, D. C. Fourth Saturday, October to May.

New Orleans Obstetrical and Gynecological Society. *President,* E. L. Zander. *Secretary,* Eugene Countiss, 921 Canal St., New Orleans, La. Meetings held every other month.

St. Louis Gynecological Society. *President,* S. A. Weintraub. *Secretary,* Joseph A. Hardy, Jr., 4952 Maryland Ave., St. Louis, Mo. Second Thursday, October, December, February, and April.

San Francisco Gynecological Society. *President,* T. Henshaw Kelly. *Secretary,* R. Glenn Craig, 490 Post Street, San Francisco, Calif. Regular meetings held second Friday in month, University Club, San Francisco, or Claremont Country Club, Oakland, Calif.

Texas Association of Obstetricians and Gynecologists. *President,* Roy Grogan. *Secretary,* J. McIver, 714 Medical Arts Building, Dallas, Texas.

Michigan Society of Obstetricians and Gynecologists (formerly the Detroit Obstetrical and Gynecological Society). *President,* Norman F. Miller. *Secretary,* Harold C. Mack, 955 Fischer Bldg., Detroit, Mich. Meeting first Tuesday of each month from October to May (inclusive).

Obstetric Society of Syracuse Hospitals. *President,* Edward C. Hughes. *Secretary,* Nathan N. Cohen, 713 East Genesee St., Syracuse, N. Y. Meets second Tuesday of September, November, January, March, and May.

Alabama Association of Obstetricians and Gynecologists. *President,* J. M. Weldon, Mobile, Ala. *Secretary,* J. F. Williams, Ala.

San Antonio Obstetric Society. *President,* I. T. Cutter. *Secretary,* S. Foster Moore, Jr., San Antonio, Texas. Meetings held first Tuesday of each month at Gunter Hotel.

Seattle Gynecological Society. *President,* Glen N. Rotten. *Secretary,* R. Philip Smith, 1305 Fourth Avenue. Meetings third Wednesday.

Denver Obstetrical and Gynecological Society. *Secretary,* Emmett A. Mechler, 1612 Tremont St., Denver, Colo.

Wisconsin Society of Obstetrics and Gynecology. *President,* Roland S. Cron. *Secretary,* Robert E. McDonald, 425 E. Wisconsin Ave., Milwaukee, Wis. Meetings held in May and October.

San Diego Gynecological Society. *President,* Geo. D. Huff. *Secretary,* Frank Russell, 233 A Street, San Diego, Cal. Meetings held on the last Wednesday of each month.

North Dakota Society of Obstetrics and Gynecology. *President,* John D. Graham, Devil's Lake. *Secretary,* G. Wilson Hunter, 807 Broadway, Fargo, N. D.

Virginia Obstetrical and Gynecological Society. *President,* H. C. Spalding. *Secretary,* W. C. Winn, 816 West Franklin St., Richmond, Va. Next meeting, October 26, 1943, Roanoke, Va.